FORMULATION AND DEVELOPMENT OF PALIPERIDONE LIQUISOLID TABLETS

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CERTIFICATE

بسم الله الرحمن الرحيم
In the Name of Allāh, the Most Gracious, the Most Merciful

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This is to certify that the dissertation entitled **"Formulation and Development of Paliperidone Liquisolid tablets"** submitted by **Mr.P.Kanniyappan (M. Pharm II year)**, in partial fulfillment of the requirement for the Degree of **Master of Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by him, under my guidance and supervision in the Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai – 20 during the academic year 2013 – 2014.

This dissertation is forwarded to the Controller of Examinations, The Tamilnadu Dr. M.G.R. Medical University, Chennai-32.

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INTRODUCTION

CHAPTER -I

INTRODUCTION

Oral drug delivery is the simplest and easiest way of administering drugs. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that originate an effective and reproducible *in vivo* plasma concentration after oral administration (Vinay kumar *et al*., 2012).

New chemical entities do not reach the expectation and requirements because of their poor oral bioavailability due to lower dissolution rate which is the rate limiting step for hydrophobic drugs.

A most important parameter that is useful for poorly soluble drugs is the dose: solubility ratio of the drug. The dose: solubility ratio can be defined as the volume of gastrointestinal fluids necessary to dissolve the administered dose. When this volume exceeds the volume of fluids available, one may anticipate incomplete bioavailability from solid oral dosage forms. The aqueous solubility for poorly water-soluble drugs is usually less than 100 µg/ml (Vijaykumar Nagabandi *et al*., 2011).

Increasing the dissolution and bioavailability of poorly soluble drugs is a major challenge facing the pharmaceutical industry today as about 40% of potential drugs produced are almost insoluble**.** As a general rule increase in dissolution done by increase in its solubility profile, this in turn end up in increased absorption (Gandhi, *et al*., 2013 and Kamalakanan V. *et al.,* 2012).

Various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of water insoluble drug such as micronization, adsorption onto high surface area carriers, lyophilization, co-grinding, formulation of inclusion complexes, solubilization by surfactants, solid dispersions, solid solutions, hydrotrophy, inclusion of the drug solution or liquid drug into soft gelatin capsules, and co solvency.

BCS classification is a scientific framework which deals in classification of drug substances based on its aqueous solubility and intestinal permeability.

Table 1: Biopharmaceutical Classification System

(Brahmankar *et al.,* 2009)

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Among the four classifications class II and class IV drugs are those belonging to lipophillic molecules which dissolve slowly, poorly, irregularly and so have serious challenges in delivery like incomplete release from the dosage form, Poor bioavailability, increased food effects and high inpatient variability (A.A. Elkordy *et al*., 2013 and Kamalakanan V. *et al.,* 2012).

Development of Dosage Forms with Poorly Water Soluble Drugs

Various methods used to increase the solubility of poorly water soluble drugs which are given below.

Micronization

The particle size reduction technique enhance the solubility and dissolution rate of poorly water soluble drugs due to the enormous surface that is generated.

Solvent Deposition

In this method, the poorly aqueous soluble drug such as nifedipine is dissolved in an organic solvent like alcohol and deposited on an inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose evaporation of solvent.

Use of soluble Prodrug

Here the physico-chemical properties of the drug are improved by bio-reversible chemical alteration. The most common prodrug strategy involves the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility.

Solid dispersion

It involves dispersion of one or more active ingredients in an inert carrier or matrix at solid state. Melting (fusion) method, solvent evaporation method or melting evaporation methods can be employed for the preparation of the solid dispersions. The dissolution rate of the solid dispersion depends on the type of carriers used or the type of the matrix forming polymers used (A. B. Pathan et al., 2012).

Liquisolid technique

The new developed technique by Spireas liquisolid system improves the dissolution properties of water insoluble or poorly soluble drugs. The liquisolid technique is a novel concept where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained. Among them, liquisolid compacts is one of the most promising and new techniques which promotes dissolution rate of water insoluble drugs.

The term liquisolid compact refers to immediate release or sustained release tablets or capsules, combined with the inclusion of appropriate adjuvant required for tabletting or encapsulating.

Need of Liquisolid System

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity. Bioavailability of poorly water soluble

hydrophobic drugs (class II in biopharmaceutics classification system) is limited by their solubility and dissolution rate. The dissolution rate of these drugs can be improved by decreasing particle size, decreasing crystallinity, and/or increasing the surface area. Several studies have been carried out to increase the dissolution rate of drugs by decreasing the particle size, by creating nanoparticles and microparticles. However, the fine drug particles have high tendency to agglomerate due to vander Waals attraction or hydrophobicity, which both result in a decrease in surface area over time. Another way of increasing the dissolution rate is adsorption of the drug onto a high-surface area carrier. In this technique, the drug is dissolved in an organic solvent followed by soaking of the solution by a high-surface-area carrier such as silica. Here, agglomeration of the drug particles is prevented due to the binding of drug to the carrier. However, due to the presence of the residual solvent in the drug formulation, it is disadvantageous to use toxic solvents. To overcome the problem, the technique of "liquisolid compacts" is a new and promising approach towards dissolution enhancement.

Liquisolid compacts possess acceptable flowability and compressibility properties. They are prepared by simple blending with selected powder excipients referred to as the carriers and the coating materials. Many grades of cellulose, starch, lactose, etc. can be used as carriers, whereas silicas of very fine particle size can be used as coating materials. In such systems, the drug existed in a molecular state of subdivision and systems were free flowing, on-adherent, dry looking powders. This technique was successfully applied for low dose water-insoluble drugs. Due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water insoluble substances may be expected to

display enhanced drug release characteristics and, consequently, improved oral bioavailability. Since dissolution of a nonpolar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates**.** The technique of liquisolid compacts has been successfully employed to improve the in vitro release of poorly water soluble drugs such as Carbamazepine, Famotidine, Piroxicam, Indomethacin, Hydrocortisone, Naproxen and Prednisolone (A.B Pathan *et al*., 2012).

Advantages

- Huge number of Bio-Pharmaceutical classification class II drugs with high permeability, slightly or very slightly water soluble and practically insoluble liquids and solid drugs can be formulated into liquisolid systems.
- Improvement of bioavailability of an orally administered water insoluble drugs is achieved.
- This principle governs or administers the mechanism of drug delivery from liquisolid systems of powdered drug solutions and it is mainly responsible for the improved dissolution profiles exhibited by this preparations.
- In this technique, production cost is low compared to soft gelatin capsules.
- Drug is formulated in a tablet form or encapsulated dosage form and is held in solubilized liquid state, which confers developed or improved drug wetting properties thereby improving drug dissolution profiles.
- Greater drug surface area is exposed to the dissolution medium.
- This liquisolid system is specifically for powdered liquid medications.

- These liquisolid systems formulate into immediate release or sustained release dosage forms.
- Optimized sustained release, liquisolid tablets or capsules of water insoluble drugs demonstrate constant dissolution rates (zero order release).
- It is used in controlled drug delivery systems.
- Drug can be molecularly dispersed in the formulation.
- Drug release can be modified using suitable formulation ingredients.
- Capability of industrial production is also possible.
- Enhanced bioavailability can be obtained as compared to conventional tablets.
- Differentiate the dosage form by admixture of colour into liquid vehicle.
- To minimize excipients in formulation compare with other formulations like solid dispersions.
- Omit the process approaches like nanonisation, micronization techniques (Syed *et al*., 2012 and Arya *et al*., 2011).

Disadvantages

- Formulation of high dose lipophilic drugs the liquisolid tablet is one of the limitations of this technique.
- In order to achieve acceptable flowability and compactability for liquisolid powder formulation, high levels of carrier material and coating materials should be added. This will increase the weight of tablets to above one gram which makes them difficult to swallow. Consequently, it is impossible with conventional tablet methods to convert high dose to liquisolid tablets with a tablet weight of less than 50mg. Dissolution profile enhancement occurs in the

presence of low levels of hydrophilic carrier, where coating material is not significant (A. B. Pathan *et al*., 2012).

Limitations

- Not applicable for formulation of high dose insoluble drugs.
- If more amount of carrier is added to produce free-flowing powder, the tablet weight increases to more than one gram which is difficult to swallow.
- Acceptable compression properties may not be achieved since during compression liquid drug may be squeezed out of the liquisolid tablet resulting in tablets of unsatisfactory hardness.
- Introduction of this method on industrial scale and to overcome the problems of mixing small quantities of viscous liquid solutions onto large amounts of carrier material may not be feasible (Sambasiva Rao. A *et al*., 2011).

Principle of Liquisolid Compacts

Important terminologies in Principle

Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in suitable non-volatile solvent systems.

Liquisolid system refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into dry, nonadherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

Carrier material refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption.

Coating material refers to a material possessing fine and highly adsorptive particles, such as various types of silica, which contributes in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid.

With the liquisolid technology, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material (Fig. 1) (Baby *et al*., 2012)

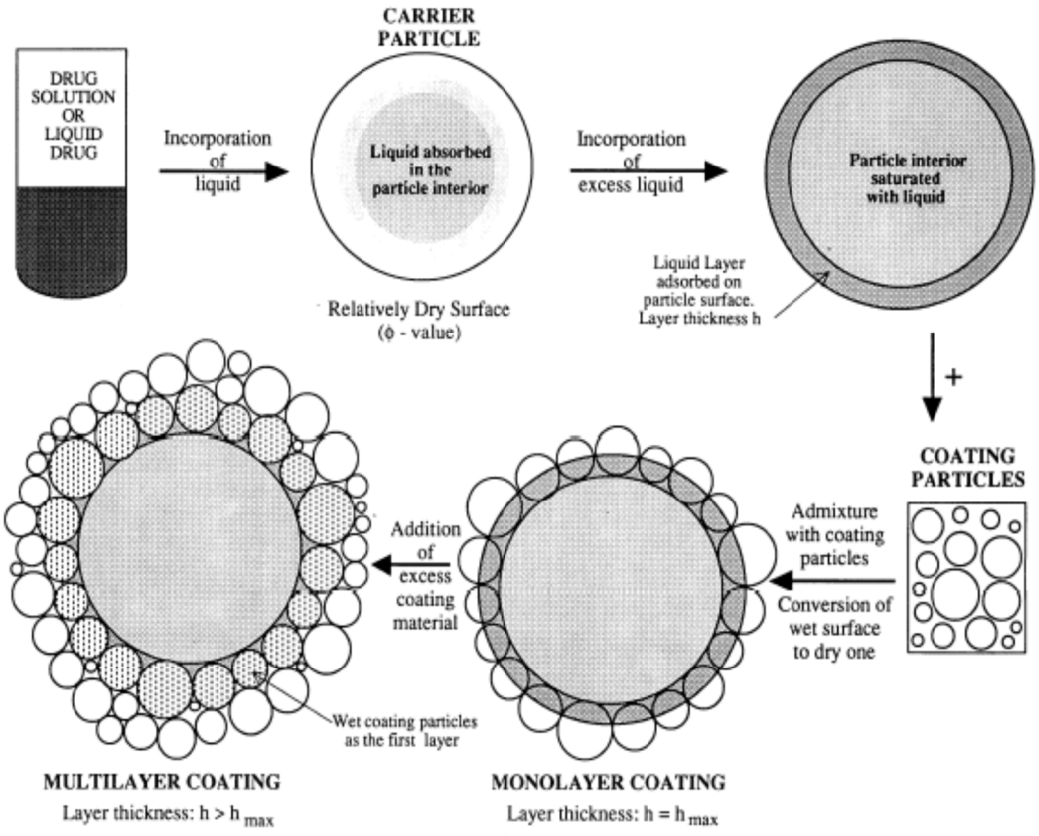


Figure 1: Schematic representation of liquisolid systems.

Inert, preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerine are best

suitable as liquid vehicles. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained. Usually, microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material. Various excipients such as lubricants and disintegrants may be added to the liquisolid system to produce liquisolid compacts (Fig. 2) (Syed *et al*., 2012)

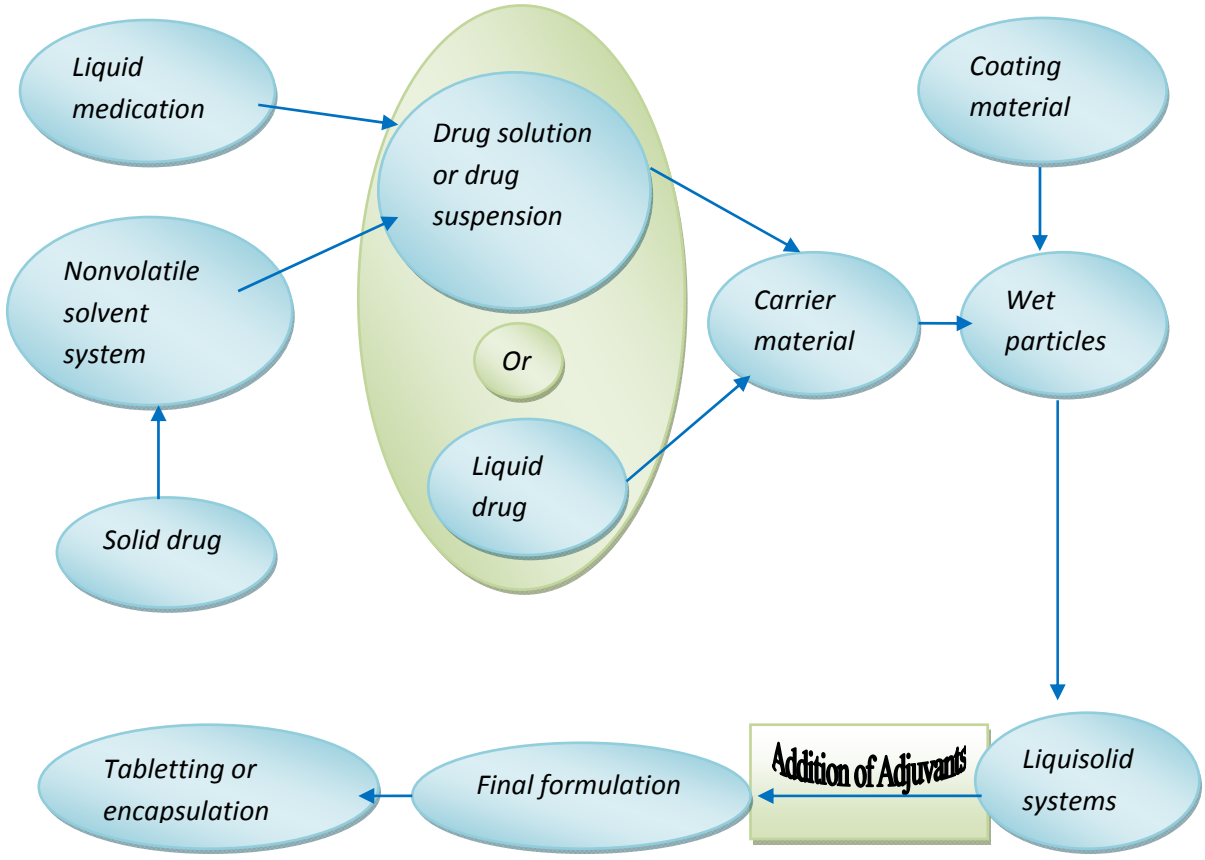


Figure 2: Schematic outline of the steps involved in the preparation of liquisolid compacts.

Comparison of wettability between conventional tablet and liquisolid tablets

The wettability of the tablets by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid tablets. Nonvolatile solvent present in the liquisolid compacts facilitates wetting of drug particles by decreasing interfacial tension between tablet surface and dissolution medium (Fig. 3) (Kisan Jadhav R *et al*., 2011).

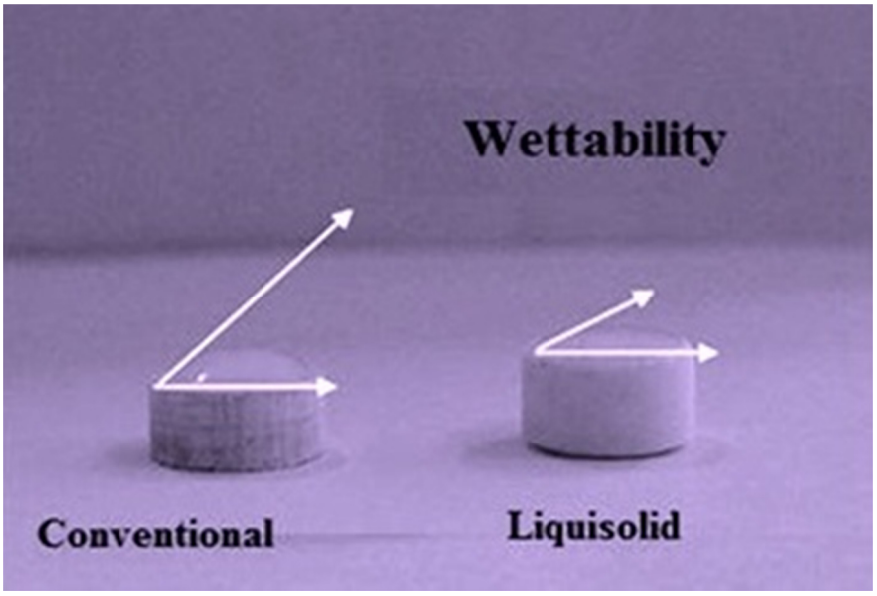


Figure 3: This figure shows lower contact angle of liquisolid tablets than the conventional tablets and thus improved wettability.

Classification of liquisolid system

A. Based on the type of liquid medication contained therein, liquisolid systems may be classified into three sub-groups

1. Powdered drug solutions
2. Powdered drug suspensions
3. Powdered liquid drugs

Powdered drug solutions and *suspensions* may be produced from the conversion of *drug solutions* or *drug suspensions* into liquisolid systems and *powdered liquid drugs* are produced from the formulation of liquid drugs into liquisolid systems.

B. Based on the formulation technique used, liquisolid systems may be classified into two categories namely,

1. Liquisolid compacts
2. Liquisolid Microsystems

The term "***liquisolid compacts*"** refers to immediate or sustained release tablets or capsules prepared, combined with the inclusion of appropriate adjuvants required for tabletting or encapsulation, such as lubricants, and for rapid or sustained release action, such as disintegrants or binders, respectively.

The term **"*liquisolid Microsystems*"** refers to capsules prepared by combining the drug with carrier and coating materials; combined with inclusion of an additive resulting in a unit size may be as much as five times that of liquisolid compacts (Sambasiva Rao *et al*., 2011 and Shashidher Burra *et al*., 2011).

Mechanisms of enhanced drug release from liquisolid systems

Several mechanisms of enhanced drug release have been postulated for liquisolid systems. The three main suggested mechanisms include an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Formation of a complex between the drug and excipients or any changes in crystallinity of the drug could be ruled out using DSC and XRD measurements.

a. Increased drug surface area

If the drug within the liquisolid system is completely dissolved in the liquid vehicle it is located in the powder substrate still in a solubilized, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets.

Accordingly, with increasing drug content exceeding the solubility limit and thus, increasing fraction of undissolved drug in the liquid vehicle the release rate decreases. With various drugs it could be shown that the release rates are directly proportional to the fraction of the molecularly dispersed drug (*FM*) in the liquid formulation. *FM* is defined by the ratio between the drug's solubility (*Sd*) in the liquid vehicle and the actual drug concentration (*Cd*) in this vehicle carried by each system. Therefore:

$$F\,M = Sd\,/Cd$$

Where $FM = 1$ if $Sd \geq Cd$

Accordingly, lower *FM*-values and higher fraction of undissolved drug in the liquid vehicle, respectively, are not sufficient to increase percentage of drug released at 30 min. However, this may not be transferred to other time points of drug release.

b. Increased aqueous solubility of the drug

In addition to the first mechanism of drug release enhancement it is expected that *Cs*, the solubility of the drug, might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid tablets is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. However, at the solid/liquid interface between an individual liquisolid primary

particle and the release medium it is possible that in this microenvironment the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a co-solvent. The overall increase in the solubility of drugs caused by liquisolid systems was confirmed.

c. Improved wetting properties

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liquisolid primary particles is improved. Wettability of these systems has been demonstrated by measurement of contact angles and water rising times (Arya *et al*., 2011)

Methodology

Spireas et al proposed the new mathematical model in accordance to retain good flow behaviour and compressibility to design the formulation for Liquisolid technique. Mandatory requirements for this technique are suitable drug candidate, suitable non-volatile solvent, carrier and coating materials. According to Spireas et al the basic properties of Liquisolid powder for good flow behaviour and compressibility proposed are "Flowable liquid retention potential" (value) and compressible liquid retention potential" (ψ value), respectively.

Flowable liquid retention potential defined as maximum weight of liquid (solvent) that can be retained per unit weight of powder (excipient) material to produce good flow. *Compressible liquid retention potential* defined as the compression force applied to produce tablets with acceptable strength without squeezing out any liquid during compression.

Excipient ratio (R) defined as Carrier to coating ratio as,

$$R = Q/q$$

Where,

Q= Carrier material

q= Coating material.

Liquid load factor (Lf) defined as weight of liquid medicament (W) to weight of carrier (w).

$$Lf = W/Q$$

The Ø value is for calculating excipients quantities.

Equation is,

$$Lf = Ø + Ø\ (1/R)$$

Where, Ø and Ø are values of carrier and coating material.

Materials required for formulation

Liquisolid system mainly includes

1. Drug candidate
2. Non volatile solvent
3. Disintegrant
4. Carrier material
5. Coating material

1. Drug candidate

These are poorly soluble or else insoluble drugs in water.

2. Non volatile Solvent

Non volatile Solvent should be inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems and compatible with having

ability to solubilise the drug. The non volatile solvent acts as a binding agent in the liquisolid formulation. Various non-volatile solvents used for the formulation of liquisolid tablets includes

1. Polyethylene glycol400
2. Propylene glycol
3. Polysorbate80
4. Capryol 90

Selection of Solvent

To select the best non-volatile solvent for dissolving or suspending the drug in liquid medication, solubility studies of drug were carried out in different non-volatile liquid vehicles. Saturated solutions were prepared by adding excess drug to the liquid vehicles and it was shaked on the shaker for 48 hours at 25◦C under constant stirring. After this period the solutions were filtered through a 0.45 μm millipore filter, diluted with distilled water and analysed by UV-spectrophotometer at respected wavelength against blank sample (blank sample containing the same concentration of the specific solvent used without drug). Three determinations were carried out for each sample to calculate the solubility of drug. Some of the solvents mentioned can be incorporated to formulate Liquisolid tablets viz. Poly ethylene glycol (PEG 200, 400, 600), Propylene Glycol, Polysorbate 80, Glycerol, Spans, Polyoxyl 35 castor oil, capryol 90 and poloxamer 181. The solvent should have the characteristic of a non-toxic and non volatile solvent. The formulation liquisolid compacts should neither enhance the dissolution rates nor retard the dissolution rates of the drug it depends upon the selection of solvent and properties of the chemical entities. Prior to selection of solvent selection in the formulation there is need to check the saturation solubility

with selected non-volatile solvents. From saturation solubility of solvent the one which has enhance rate of dissolution, the solvent with minimum solubility retards the rate of drug release

3. Disintegrant

Superdisintigrants increases the rate of drug release, water solubility and wettability of liquisolid granules. Mostly superdisintigrants like sodium starch glycolate, croscarmelose sodium, pre gelatinized starch and crosspovidone are used.

4. Carrier Materials

Carrier material should be porous material possessing sufficient absorption properties which contributes in liquid absorption. The carrier and coating materials can retain only certain amounts of liquid and at the same time maintain acceptable flow and compression properties hence, increasing moisture content of carrier's results in decreased powder flowability. Various grades of microcrystalline cellulose such as avicel PH 102, avicel PH 200 and experimental grade of granular amorphous cellulose, lactose used as carrier materials.

5. Coating Materials

Coating material should be a material possessing fine and highly adsorptive particles which contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid. Coating material is required to cover the surface and maintain the powder flowability. Coating material includes silica (Cab-O-Sil) M5, Aerosil 200 (Rajesh K. e*t al*., 2011).

Characterization of liquisolid tablets

Table 2: Characterization of liquisolid tablets (Sambasiva Rao *et al*., 2011)

Characterization	Purpose
1. UV-spectrophotometer	Assay & uniformity content
2. Infrared Spectroscopy	Interaction studies
3. Powder X-Ray Diffraction Analysis (XRD)	Crystalline Properties
4. Differential Scanning colorimetry (DSC)	Interaction studies, polymorphism
5. *In vitro* Dissolution studies	Release Properties of drug
6. SEM analysis	Surface morphology

Importance of carrier and coating material ratio (R)

Liquisolid systems pre-compression and drug release properties increase with powder excipient ratios (R) from 5:1 to 50:1. A linear relationship exists between the liquid load factors Lf and the reciprocal powder excipient ratios (1/R) required producing acceptable flowing and readily compressible liquid and powder admixtures. The linear relationship between Lf and the 1/ R plot of liquisolid systems possesses Y intercept and slope equal to the Φ values of the cellulose carrier powder and silica coating material.

Liquisolid tablets dissolution rate profiles are affected by powder excipients ratio R in which results exhibited within the 5 minutes of the dissolution process against the r values 5 to 20 range R values. The dissolution rates increased almost proportionally to R until reaching an apparent maximum plateau at powder excipient ratios greater than 20.

Lower R values of liquisolid tablets contain relatively smaller amounts of carrier powder (cellulose), a large amount of fine coating particles (silica), and the ratios of their liquid medication per powder substrate are relatively higher.

From the low liquid and powder ratios, a high presence of cellulose and low presence of silica may be directly associated with enhanced wicking, disintegration, and degradation properties. Low R values should justifiably display relatively poor dissolution profiles. After disintegration, low R values of liquisolid tablets are overloaded with liquid medication producing the primary particles.

On other hand, in some cases, the drug diffusion through the primary particles may be rapid and might lead to overwhelming (solubility- wise) of the stagnant dissolution layers with drug. After maximum levels of dissolution are reached at 35 to 45 R values, a slight gradual decrease of dissolution rate occurs with increasing powder excipient ratios.

For R values higher than 50, they may be attributed to the slower diffusion of the liquid medication through the numerous porous carrier powder particles into which the drug solution has been embedded during the formulation process. To determine the effect of different type of carriers such as Avicel pH 102, lactose, starch or sorbitol, dissolve in solution containing 10% w/w of drug in liquid medication. Carriers show the potential to absorb the liquid medication. Large amounts of these carriers are necessary for regenerating liquid medication to dry looking and non adherent powder.

Avicel PH 102 showed better results, due to its large specific area in comparison with other carriers such as lactose and starch.

Type of carrier might affect the unit size of liquisolid tablets. Higher Avicel PH 102 concentrations show uniform distribution of the drug by either adsorption onto or absorption into the carrier. Between the hydrogen groups, hydrogen bonds on adjacent cellulose molecules in Avicel PH 102 may account exclusively for the strength and cohesiveness of compacts. Avicel PH 102 compressibility and compactness characteristics can be explained by the nature if crystalline cellulosic particles themselves which are held together by hydrogen bonds which when compressed, are deformed plastically and a strong compact is formed due to the extremely excessive number of surfaces brought into contact during the plastic deformation, and the strength of the hydrogen bonds are formed.

Non-volatile liquid vehicles such as propylene glycol, polyethylene glycol 400, tween 80 and capryol 90 were shown to facilitate wetting of drug particles by decreasing interfacial tension between dissolution medium and the tablet surface. Increase in the wetting properties of liquisolid tablets by the dissolution media is one of the main reasons for the dissolution rate enhancement. High R values 30 to 60 evidence better uniform distribution of the drug in the carrier material. (Shashidher Burra *et al*., 2011)

Dissolution studies on liquisolid tablets

Tablets should be sufficiently hard to resist breaking during normal handling and yet quickly disintegrate properly after swallowing.

Dissolution rate (DR) is explained according to the "Noyes – Whitney" equation and "diffusion layer model" dissolution theories.

$$\mathbf{DR = (D/h)\ S\ (Cs- C)}$$

According to this equation, stagnant diffusion layer thickness is h, and formed by the dissolving liquid around the drug particles. D is the diffusion coefficient of the drug molecules transported through it, S is the surface area of the drug available for dissolution, C is the drug concentration in the bulk of the dissolving medium, and Cs is the saturation solution of the drug in the dissolution medium. Dissolution tests for liquisolid tablets were done at constant rotational speed and in identical dissolution media, thus allowing estimation of the thickness of the stagnant diffusion layer (h). From this equation, dissolution rate is directly proportional not only to the concentration gradient of the drug in the stagnant diffusion layer (Cs- C), but also to its surface area (S) available for dissolution.

For estimation and comparison, drug dissolution rates (DR) of drug were used, with amount of drug dissolved per min presented by each tablet formulation during the first 10 minutes (Shashidher Burra *et al*., 2011).

$$\mathbf{D\,R} = \frac{\mathbf{(M \times D)}}{\mathbf{1000}}$$

Where,

M = Total amount of pure drug in each tablet

D = Percentage of drug dissolved in the first 10 minutes

Applications

1. Rapid release rates are obtained in liquisolid formulations

2. These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs.

3. Sustained release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.

4. Solubility and dissolution enhancement.

5. Designing of controlled release tablets.

6. Application in probiotics.

CHAPTER II

LITERATURE REVIEW

CHAPTER-II

LITERATURE REVIEW

Ahmed S. Abdul Jabbar et al., 2013, formulated and evaluated piroxicam liquisolid compact different liquisolid compacts were prepared using a mathematical model to calculate the required quantities of powder and liquid ingredients to produce acceptably flowable and compressible admixture. The liquisolid formulation which might be attributed to the formation of hydrogen bonding between the drug and liquid vehicle this resulted in drug dissolution enhancement.

Amal Ali Elkordy et al., 2013, studied spironolactone release from liquisolid formulations prepared with capryol 90, solutol HS-15 and kollicoat SR 30D as non-volatile liquid vehicles were used in the design of spironolactone liquisolid formulations, capryol 90, synperonic PE/L61 in combination with solutol HS-15 at a ratio of 1:1 and kollicoat SR 30D. Spironolactone liquisolid formulations were tested according to British Pharmacopoeia (BP) quality control tests. Liquisolid powder formulations formulated from a combination of synperonic PE/L61- solutol HS showed highest dissolution. The liquid vehicles used with spironolactone liquisolid formulations enhanced drug dissolution rate.

Jarag Ravindra Jagannath et al., 2013, formulated and evaluated sustained release liquisolid tablets of metoprolol succinate. This is directed towards the development of liquisolid compact for the production of sustained release tablet of water soluble drug. Liquisolid compacts were prepared by using Tween 80 as the liquid vehicle or non-volatile solvent. Avicel PH 102 as absorbing carrier and Aerosil 200 as adsorbing coating material. Tween 80 has plasticizer effect by which it can reduce the glass

transmission temperature of polymer and impart flexibility in sustaining the release of drug from liquisolid matrices. The results showed that wet granulation had a remarkable impact on the release rate of drug from liquisolid compacts reducing the release rate of drug from liquisolid compacts.

Gandhi K.J. et al., 2013, formulated, characterized and evaluated the liquisolid tablet containing pioglitazone HCl. The invitro release pattern of liquisolid tablets and directly compressed tablets were studied using USP-2 apparatus. The study concludes that the liquisolid technique is a promising alternative and best suitable method for enhancing solubility.

Pandey A. et al., 2013, carried out project on dissolution rate enhancement of BCS Class II drug paliperidone by spray drying. The technique adopted is very well used industrially for preparing amorphous composition of poorly soluble crystalline drugs. In case of spray drying PAL with different classes of hydrophilic carriers (different grades of polyvinyl pyrolidones [PVPs, plasdones] and cellulosic polymers) were taken. Significant enhancement in dissolution rate was observed with the prepared spray dried compositions and out of three grades of plasdone; plasdone K12 demonstrated the maximum enhancement in rate of release of PAL. Spray drying of PAL with plasdones, especially plasdone K12 reduced drug crystallinity, increased rate and extent of dissolution.

Pande V. V. et al., 2013, enhanced dissolution rate of rosuvastatin calcium by liquisolid compact technique. In this technique, liquid medications of water insoluble drugs in non-volatile liquid vehicles can be converted into acceptably flowing and compressible powders. As liquisolid compacts demonstrated significantly higher drug

release rate, they lead to a conclusion that it could be a promising strategy by improving the dissolution of poor water soluble drugs and immediate release solid dosage forms.

Amal Ali Elkordy et al., 2012, performed liquisolid technique to enhance and sustain griseofulvin dissolution effect by using non-volatile liquid vehicles. They studied the effects of different liquid vehicles on release characteristics. Fast dissolution tablets were prepared using three different non-ionic surfactants namely cremophor EL, synperonic PE/L61 and capryol 90; on the contrary kollicoat SR 30P were used for production of sustained release formulations. Avicel PH102 and cab-O-sil M5 were used as a carrier and coating materials respectively. Cremophor EL showed the best dissolution enhancement with % PE of about 90% compared to only 23% of conventional tablets.

Burra shashidher et al., 2012, formulated and evaluated carvedilol liquisolid tablets. A novel powder solution technology involves absorption and adsorption efficiency, which makes use of liquid medications, admixed with suitable carriers, coating materials and formulated into a free flowing, dry looking, non-adherent and compressible powder forms. The crystalline state of drug is changed to amorphous state due to liquisolid formation and is confirmed by both DSC and X-ray diffraction results. The amorphous form exhibited increased wetting properties because of subsequent increased surface area of the particle size.

Shah C.V.et al., 2012, designed, developed and optimized valsartan liquisolid tablets using Box – Behnken design. This study was designed to optimize and evaluate the effects of different formulation variables. Amount of liquid (X_1),ratio of carrier to

coating material (X_2) and amount of magnesium oxide (X_3) on angle of repose (Y_1), hardness (Y_2) and invitro release (Y_3) of formulation using three level Box –Behnken stastical design. The non–linear quadratic model generated by the design in the form of $Y=A_0 + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_1X_2 + A_5X_2X_3 + A_6X_1X_3 + A_7X1^2 + A_8X_2^2 + A_9X_3^2 + E$, where y is the measured response surface plots were depicted based on the equation given by the model.

Dnyanesh walunj et al., 2012, formulated and evaluated tamoxifen citrate liquisolid compacts were prepared using a mathematical model to calculate the required quantities of powder and liquid ingredients to produce acceptably flowable and compressible admixture. Avicel PH 102, Aerosil 200, croscarmellose sodium and propylene glycol were employed as carrier, coating material, disintegrant and non-volatile solvent respectively for preparing liquisolid compact. This study was concluded that liquisolid technique is a promising alternative for improvement of dissolution property of water insoluble drugs.

Sateesh kumar Vemula et al., 2012, enhanced dissolution rate of nimesulide by liquisolid technique. Liquisolid tablets were prepared by using polyethylene glycol 400 as a non-volatile liquid vehicle, microcrystalline cellulose, hydroxyl propyl methyl cellulose E-15, starch were used as carrier materials and silica gel as coating material in different ratios. *Invitro* dissolution profiles of liquisolid formulations were studied and compared with conventional formulation in pH7.4 phosphate buffer and it was found that liquisolid tablets formulated with microcrystalline cellulose showed significant higher drug release rates than conventional tablets due to increase in wetting properties.

Sidharth patil et al., 2012, formulated and evaluated liquisolid tablets of non steroidal anti inflammatory drug ibuprofen were prepared by using microcrystalline cellulose (Avicel PH 101) as a carrier material, silica gel as coating material, poly ethylene glycol 400 as non – volatile water miscible liquid vehicle and 5%sodium starch glycolate used as super disintegrating agent. The results showed that liquisolid formulations of ibuprofen exhibited higher percentage of drug release than marketed formulation.

Kamalakannan V. et al., 2012, formulated and evaluated tinidazole liquisolid tablets. A liquisolid system is formed by converting a liquisolid formulation into a dry, free-flowing and compressible powder mixture with selected carrier material and coating material. Liquisolid tablet formulation by using 20:1 ratio of powder excipients ratio (480mg of Avicel and 24mg of Cab-O-sil) and 100% w/w tinidazole in PG 600 solvent were satisfying the requirements.

Sirisha V.N.L. et al., 2012, prepared and evaluated (*in vitro*) liquisolid compacts of glibenclamide. Liquisolid tablets were prepared by using PEG 400 as non- volatile liquid vehicles and Avicel PH 101, Aerosil as carrier and coating materials respectively. The properties of glibenclamide particles were changed by dispersing the drug particles in a non–volatile liquid vehicle, which in turn increases the wetting properties and surface area of drug particles, and hence improve the dissolution profiles and oral bioavailability of the drug.

Lakshmi P.K. et al., 2011, prepared and comparatively evaluated liquisolid compacts and solid dispersions of valsartan. Liquisolid technology and solid dispersion by kneading method used to improve the solubility of the drug by using non-volatile

solvents. Various non-volatile solvents were used such as PG, PEG and glycerin. The carrier and coating material play an important role in improving the solubility of the drug. Solid dispersion by kneading method is another attempt to improve solubility. Various carrier materials were used such as PVP K30, PEG 6000 and mannitol. These carriers were used in various ratios to improve its solubility. The results concluded that the liquisolid compacts enhanced the solubility of valsartan in comparison to traditional solid dispersion method.

Vijayakumar Nagabandi et al., 2011, formulated, developed and evaluated liquisolid systems to improve the dissolution rate of ketoprofen using different carrier materials such as microcrystalline cellulose (Avicel PH101), starch, dicalcium phosphate, lactose and silica gel as coating material. Polyethylene glycol 400 was used as non-volatile water miscible liquid vehicle. The ratio of carrier to coating material was kept constant in all formulations of ketoprofen which exhibited higher percentage of drug release than marketed formulation.

Vijayakumar Nagabandi et al., 2011, formulated, developed and evaluated liquisolid systems to improve the dissolution rate of naproxen with two different liquid vehicles, namely polyethylene glycol 400 and propylene glycol. Two different carrier materials were used namely microcrystalline cellulose (Avicel PH101) and dicalcium phosphate. Silica gel as coating material and sodium starch glycolate as disintegrating agent in all formulations. The results showed that liquisolid formulations of ketoprofen exhibited higher percentage of drug release than marketed formulation.

Ali Nokhodchi et al., 2010, studied the effect of co solvent and HPMC on theophylline release. Liquisolid tablets were prepared by mixing liquid medication with silica. Eudragit RL or RS followed by the compaction of the mixture. For comparison purposes physical mixtures of all ingredients were prepared. The effect of liquid medication and HPMC concentration on drug release was investigated. The sustained release action of HPMC was enhanced in liquisolid compacts in comparison to simple sustained release matrix tablets.

Amal A. Elkordy et al., 2010, developed liquisolid systems to improve the dissolution rate of furosemide were prepared using microcrystalline cellulose (Avicel PH 101)as carrier and fumed silica (Cab-O-sil M-5) as coating material. Polyethylene-polyoxypropylene-polyoxyethylene block copolymer (Synperonic PE/L81) 1, 2, 3 propranolol, homopolymer, (a2) 9-octadecenoate (caprol PGE-860) and polyethylene glycol 400 (PEG 400) were used as non-volatile water miscible liquid vehicles. The results showed that all formulations exhibited higher percentage of drug dissolved in water (pH6.4-6.6) compared to that of acidic medium (pH1.2). Liquisolid compacts containing synperonic PE/L81 showed higher release rate at different pH values. Formulations with PEG 400 displayed lower drug release rate compared to conventional tablet.

Amrit B. Karmarkar et el., 2010, evaluated (*in vitro*) dissolution profile comparison methods of sustained release tramadol hydrochloride with marketed sustained release tablets. Liquisolid sustained release formulations were prepared by using HPMC K4M as a sustained release agent. Liquisolid compacts were evaluated .The dissolution profile followed the Peppas model as “best fit”. Two-way ANOVA results revealed a significant difference in dissolution profiles. This systematic

approach to producing a formulation was found to help with analyzing the sustained release of tramadol hydrochloride.

Dinesh M. Pardhi et al., 2010, developed liquisolid technique for enhancement of dissolution properties of carvedilol. The invitro release pattern of liquisolid compacts and directly compressed tablets were studied using USP-2 apparatus. From this study it concludes that the liquisolid technique is a promising alternative for improvement of dissolution property of water insoluble drugs.

Khalid M. El-Say et al., 2010, formulated and evaluated rofecoxib liquisolid tablets. The effect of powder substrate composition on the flow ability and compressibility of liquisolid compact were evaluated specifically several liquisolid formulation containing 25mg rofecoxib using different carrier to coating ratios in their powder substrates and fixed liquid medication were prepared. From the previous results, it was concluded that addition of 10 % Cab-O-Sil and 5% magnesium oxide improved both the flow ability and compressibility of tested rofecoxib powders. These two substances change the flow ability from bad flow to satisfactory flow. The prepared liquisolid tablets showed higher dissolution profile than the three studied commercial tablet.

Shashibher Burra et al., 2010, enhanced the solubility and dissolution rate of furosemide through liquisolid technique. The drug dissolution was tested using different dissolution media such as 1.2pH, 5.4pH, 6.8pH, 7.4pH. The results showed that liquid solid tablets have higher drug dissolution rates than the conventional and directly compressible tablet.

Sanjeev raghavendra Gubbi et al., 2010, formulated and characterized atorvastatin calcium liquisolid compact were prepared using a mathematical model for calculating required quantities of powder and liquid ingredients to produce an acceptably flowable and compress able admixture. Avicel PH102, Aerosil 200 and Explotab were employed as carrier, coating material and disintegrant respectively. This study shows that the liquisolid technique is a promising alternative for improvement of the dissolution rate and oral bioavailability of water insoluble drugs confirmed by estimating the pharmacokinetic parameters *in vivo* in rabbits.

Amrit B. Karmarkar et al., 2009, enhanced dissolution rate of fenofibrate using liquisolid tablet technique. Liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be easily converted into powders with acceptable flow properties and compression behavior by using powder excipients. Enhanced drug release profiles due to increased wetting properties and surface of drug available for dissolution was obtained in case of liquisolid tablets.

Amal A. Elkordy et al., 2009, formulated and evaluated the effects of liquisolid formulations on dissolution of naproxen with three different liquid vehicles namely cremophor EL, synperonic PE/L61 and polyethylene glycol 400 at two drug concentrations 20% w/w and 40% w/w. Avicel PH102 was used as a carrier material, Cab-O-sil M5 as a coating material, maize starch as a disintegrant. Liquisolid tablets formulated with cremophor EL at drug concentration of 20% w/w produced high dissolution profile with acceptable tablet properties.

Sanjeev Gubbi et al., 2009, performed liquisolid technique for enhancement of dissolution properties of bromhexine hydrochloride. Different LS compacts were

prepared using a mathematical model to calculate the required quantities of powder and liquid ingredients to produce acceptably flowable and compressible mixture. The prepared LS compacts were evaluated. From this study it was concluded that the LS technique is a promising alternative improvement of dissolution property for water insoluble drugs.

Yadav V.B. et al., 2009, improved solubility and dissolution of indomethacin by liquisolid compaction and granulation technique. In the liquisolid system IM was dispersed on polyethylene glycol 400(PEG 400) as a non-volatile liquid vehicle. Microcrystalline cellulose (Avicel PH102) and dibasic calcium phosphate (DCP) were used as a carrier; hydroxypropyl methyl cellulose (HPMC) as coating material and sodium starch glycolate (SSG), croscarmellose sodium (CCS) were used as disintegrants. It was observed that the drug release rate, water solubility and wettability of liquisolid granules containing super disintegrants were on higher side compared to liquisolid granules without super disintegrants.

Ali Nokhodchi et al., 2008, carried out liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices. The drug was dispersed in polysorbate 80 as liquid vehicle. Then the binary mixture of eudragit RL or RS (carrier) and silica (coating material) was added to the liquid medication under continuous mixing in a mortar. The final mixture was compressed using a manual tableting machine. The release rate of propranolol HCl from liquisolid compacts was compared with that of conventional tablets. The drug prepared by liquisolid technique showed greater retardation properties in comparison with conventional tablets. This investigation provided evidence that polysorbate 80 (Tween 80) has important role in sustaining the release of drug from liquisolid matrices.

Ali Nokhodchi et al., 2007, studied liquisolid technique as a tool for enhancement of poor water soluble drugs and evaluated their physiochemical properties. Different formulations of liquisolid tablets, using different co-solvents, (non-volatile solvents) were prepared and the effect of aging on the dissolution behavior of indomethacin liquisolid compacts was investigated. Dissolution test was carried out at two different pH, 1.2 and 7.2 to simulate the stomach or intestine fluid respectively. Liquisolid compacts containing propylene glycol as vehicle produced higher dissolution rates in comparison with liquisolid compacts containing PEG 400 or Tween 80 of the same concentration.

Ali Nokhodchi et al., 2007, enhanced the dissolution rate of high dose water insoluble drug (carbamazepine) using liquisolid technique. Different liquisolid formulations of drug were accomplished by dissolving the drug in the non–toxic hydrophilic liquids and adsorbing dissolution on to the surface of silica. In order to reduce the amounts of carrier and Aerosil in liquisolid formulations some additives namely polyvinyl pyrolidone (PVP), hydroxypropyl methyl cellulose (HPMC) and polyethylene glycol (PEG 35000) were added to liquid medication to increase loading factor. The effects of various ratios of carrier to coating material, PVP concentration, effect of aging and type of carrier on dissolution rate of liquisolid compacts were studied. The results showed that drug loading factors was increased significantly in the presence of additives. It was shown that microcrystalline cellulose had more liquid retention potential in comparison with lactose and the formulations containing microcrystalline cellulose as carrier, showed higher dissolution rate. By decreasing the ratio of microcrystalline cellulose to silica from 20 to 10, an improvement in dissolution rate was observed.

Dina Louis et al., 2007, improved the dissolution properties of carbamazepine through application of liquisolid tablet technique. Avicel PH 102 and Aerosil 200 were used as carrier and coating material respectively and Explotab was used as disintegrant to prepare four tablet formulae, out of which formula 1 was successfully compressed into tablets. The prepared tablets showed good wettability, rapid disintegration and acceptable dissolution rate comparable to the generic product.

Nokhodchi A. et al., 2005, enhanced the dissolution rate of piroxicam using liquisolid compacts. The dissolution behavior of drug from liquisolid compacts was investigated in simulated gastric fluid (SGF pH1.2) and simulated intestinal fluid (SIF pH7.2). The results showed that liquisolid compacts demonstrated significantly higher drug release rates than those of conventionally made. This was due to an increase in wetting properties and surface of drug available for dissolution.

Khaled A. Khaled et al., 2001, evaluated (*in vivo*) hydrochlorothiazide liquisolid tablets in beagle dogs. The drug was administered orally as a single 25mg dose of commercial and liquisolid tablets on two occasions in a randomized two-way cross over design. The absolute bioavailability of the drug from the liquisolid tablets was 15% higher than that from the commercial one. The parametric 90% confidence intervals for the different parameters were higher than the commonly expected intervals for bioequivalency, indicating greater bioavailability of the liquisolid tablets.

Spiro Spireas et al., 1998, enhanced prednisolone dissolution properties using liquisolid compacts. According to the new formulation method of liquisolid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non – volatile liquid vehicles can be converted into acceptably flowing and

compressible powders by blending with selected powder excipients. Liquisolid compacts demonstrated significantly higher drug release rates, in different dissolution media and volumes, compared to tablets prepared by the direct compression method.

CHAPTER III

AIM OF THE WORK

CHAPTER - III

AIM OF THE WORK

The poor dissolution rate of water insoluble drug is a major impediment to the development of pharmaceutical dosage forms. The oral absorption of drugs is most often controlled by dissolution in the gastrointestinal tract. Different methods are employed to improve the dissolution characteristics of poorly water soluble drugs, like solubilization, pH adjustment, co-solvents, microemulsion, particle size reduction, use of surfactant as a solubilizing agent, prodrug approach etc. Amongst these the most promising method for promoting dissolution is the use of the liquisolid system.

Liquisolid system refers to formulations formed by conversion of oily liquid drugs and solutions or suspensions of water insoluble solid drugs in non-volatile solvents into dry, non-adherent, free flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials.

Schizophrenia is one of the functional disorders of psychosis. No underlying cause can be defined for this; memory and orientation are mostly retained but emotion, thought and behavior are seriously altered. Schizophrenia is also known as the split mind i.e. splitting of perception and interpretation from reality-hallucination, inability to think coherently.

Schizophrenia can be treated by various drugs like risperidone, clozapine, olanzapine, haloperidol, trifluperidol, paliperidone etc. Paliperidone is a prescription

drug used for the treatment of schizophrenia. Paliperidone belongs to atypical antipsychotics.

Paliperidone is a class II drug of BCS classification; hence it has a low solubility and low permeability. Due to the low solubility it has a low oral bioavailability. Paliperidone has 28% oral bioavailability.

To overcome the drawbacks, various techniques are employed to enhance the dissolution of water insoluble drug. Among these the “liquisolid” is a newly developed technique. As the drug is in the form of liquid medication, it is in either solubilized or molecularly dispersed state. Due to increased wetting and surface area for dissolution, liquisolid tablets of water insoluble drugs may show improved dissolution properties and in turn increases bioavailability.

The aim of present study is to formulate liquisolid tablets of paliperidone using non-volatile liquid Tween 80, Avicel PH102 as a carrier and Aerosil 200 as a coating material. The best formulation selection is on the basis of release pattern and is to be compared with directly compressed tablet and pure drug.

CHAPTER IV

PLAN OF WORK

CHAPTER - IV

PLAN OF WORK

1. PREPARATION OF STANDARD CALIBRATION CURVE

a) Determination of λ_{max}

b) Preparation of calibration curve

2. SOLUBILITY STUDIES

3. PREFORMULATION (COMPATIBILITY) STUDIES

a) Infrared spectroscopic studies

4. FLOWABLE LIQUID-RETENTION POTENTIAL (Φ-VALUE) OF EXCIPIENTS

a) Determination of the angle of slide

b) Determination of flowable liquid-retention potential (ϕ-value)

5. PROCEDURE FOR PREPARATION OF LIQUISOLID POWDER

6. PREPARATION OF DIRECTLY COMPRESSED TABLETS

7. PRECOMPRESSIONAL EVALUATION OF POWDER BLEND

a) Angle of repose

b) Bulk Density

c) Tapped Density

d) Carr's Index

e) Hausner's Ratio

f) Drug content for Powder Blend

8. POSTCOMPRESSIONAL EVALUATION OF LIQUISOLID TABLETS

a) General appearance

b) Thickness

c) Hardness

d) Weight variation

e) Friability test

f) Estimation of drug content

g) Disintegration test

9. *IN VITRO* RELEASE STUDIES

10. POWDER X-RAY DIFFRACTION STUDIES

11. ASSESSMENT AND COMPARISON OF DRUG DISSOLUTION RATES

12. SELECTION AND EVALUATION OF BEST FORMULATION

a) Comparison of dissolution studies of best formulation with pure drug and directly compressed tablets

b) Infrared spectroscopic studies for best formulation

c) Differential scanning colorimetric (DSC) studies for best formulation

d) SEM analysis for best formulation

e) Stability studies

CHAPTER V

MATERIALS AND EQUIPMENTS

CHAPTER- V

MATERIALS AND EQUIPMENTS

MATERIALS	DISTRIBUTORS
Paliperidone	Orchid Pharmaceuticals, Chennai.
Propylene glycol	Indian drugs and pharmaceutical limited, Hyderabad.
Polyethylene glycol 400	Central drug house (P) Ltd, New Delhi.
Tween 80	Himedia Laboratories Pvt Ltd, Mumbai.
Capryol 90 (propylene glycol monocaprylate)	Gift Samples from Gattefosse India Pvt Ltd, Mumbai.
Talc	Nice chemicals, Kochi.
Microcrystalline cellulose	Central drug house (P) Ltd, New Delhi.
Aerosil 200 (silica)	Pharmafabrikon, Madurai.
Sodium starch glycolate	Pharmafabrikon, Madurai.
Magnesium stearate	Central drug house (P) Ltd, New Delhi.
Methanol	Astron Chemicals, Ahmedabad.

EQUIPMENTS	SUPPLIERS
Electronic Weighing Balance	A&D Company, Japan.
Single punch tablet compression machine	Cadmach Machinery Co.Pvt, Ahmadabad.
UV Visible spectrophotometer	Shimazdu UV-1700, Japan.
Digital tablet dissolution test apparatus	Lab India Disso apparatus 2000, India.
Friability test apparatus	Indian Equipment corporation, Mumbai.
Tablet hardness tester	Praveen Enterprises, Bangalore.
Vernier caliper	Linker, Mumbai.
Disintegration test apparatus	Rolex, India.
Fourier transform infrared spectroscopy	Shimadzu, Japan.
Differential scanning colorimeter	DSC Q200 V24.4 Instrument, USA.
Powder X-ray diffractometer	XD, Shimadzu, Japan.
Scanning electron microscopy	Hitachi X650, Tokyo, Japan
Magnetic stirrer	M.C.Dalal, Chennai.
Mechanical shaker	Secor, India.
Environmental Chamber	Inlab Equipments (P) Ltd, Madras.

CHAPTER VI

DRUG PROFILE

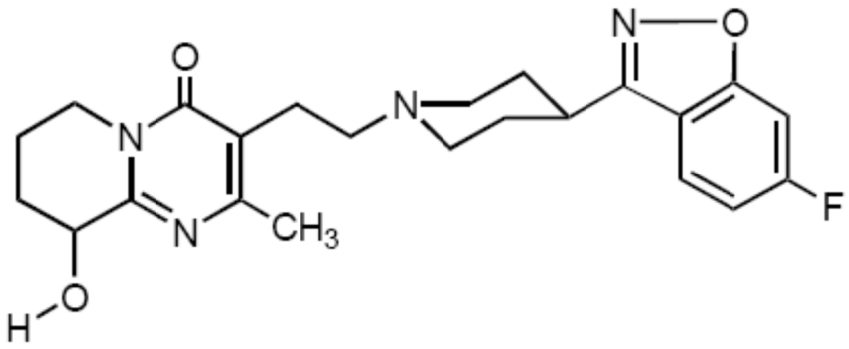
CHAPTER - VI

DRUG PROFILE

DRUG NAME : PALIPERIDONE

SYNONYM : 9-Hydroxyrisperidone

STRUCTURAL FORMULA



CHEMICAL FORMULA : C_{23} H_{27} FN_4O_3

CHEMICAL NAME

(±)-3-[2-[4-(6-fluoro-1,2benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

DESCRIPTION

Physical state	:	Solid
Colour	:	Off-white to yellow powder
Solubility	:	Paliperidone is sparingly soluble in 0.1N HCl and methylene chloride; practically insoluble in water, 0.1N NaOH, and

		hexane; and slightly soluble in N, N-dimethylformamide.
Molecular weight	:	426.49 g/mol
pKa	:	0
Log P	:	1.76
Refractivity	:	116.04
Melting point	:	168° C
Polarizability	:	45.95

MECHANISM OF ACTION

Paliperidone is the primary active metabolite of the older antipsychotic risperidone. While its specific mechanism of action is unknown, it is believed that paliperidone and risperidone act via similar if not the same pathways. It has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 (D2) and serotonin Type 2 (5HT2A) receptor antagonism.

Paliperidone is also active as an antagonist at alpha 1 and alpha 2 adrenergic receptors and H1 histaminergic receptors, which may explain some of the other effects of the drug.

PHARMACOKINETICS

Absorption

The absolute oral bioavailability of paliperidone following paliperidone administration is 28%.

Volume of distribution

Mean volume of distribution at steady-state of paliperidone is approximately 487 liters.

Protein binding

The plasma protein binding of racemic paliperidone is 74%.

Metabolism

Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, *in vivo* results indicate that these isozymes play a limited role in the overall elimination of paliperidone. Four primary metabolic pathways have been identified *in vivo*, none of which could be shown to account for more than 10% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Paliperidone does not undergo extensive metabolism and a significant portion of its metabolism occurs in the kidneys.

Route of elimination

One week following administration of a single oral dose of 1 mg immediate-release 14C-Paliperidone to 5 healthy volunteers, 59% (range 51% – 67%) of the dose was excreted unchanged into urine, 32% (26% – 41%) of the dose was recovered as metabolites, and 6% – 12% of the dose was not recovered.

HALF LIFE

The terminal elimination half life of paliperidone is approximately 23 hours.

INDICATIONS AND USAGE

Paliperidone is indicated for the treatment of schizophrenia including acute treatment and recurrence prevention. It is also indicated for the treatment of acute exacerbations of schizoaffective disorder as monotherapy and in combination with antidepressants and or mood stabilizers (lithium and valproate).

DOSAGE AND ADMINISTRATION

1.5 mg to 12 mg. The recommended dose for the treatment of schizophrenia is 6 mg once daily, administered in the morning. Some patients may benefit from lower or higher doses within the usual range of 3 mg to 9 mg once daily. Dose increases above 6 mg 1 day should be made only after clinical reassessment and generally should occur at intervals of more than 5 days. When dose increases are indicated, small increments of 3 mg/day are recommended. If required the dose may be increased to the maximum recommended dose of 12 mg once daily.

Injection 25 mg to 150 mg monthly.

DOSAGE FORMS

Tablet, extended release - Oral 3 mg

Tablet, extended release - Oral 6 mg

Tablet, extended release - Oral 9 mg

CONTRAINDICATIONS

Hypersensitivity to paliperidone or risperidone

ADVERSE REACTIONS

- Tachycardia
- Headache
- Somnolence
- Hyperprolactinemia
- Akathisia
- Orthostatic hypotension
- Parkinsonism

- Dizziness
- Weight gain
- Hyperkinesia
- Dose dependent dyskinesia
- Abdominal pain
- Tremor
- Dry mouth
- Hypersalivation
- Vomiting

OVERDOSAGE

While experience with paliperidone overdose is limited, among the few cases of overdose reported in pre-marketing trials, the highest estimated ingestion of 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and somnolence, tachycardia and hypotension and QT prolongation.

DRUG INTERACTIONS

- Centrally-acting drugs: Due to CNS effects, use caution in combination. Avoid alcohol.
- Drugs that may cause orthostatic hypotension: An additive effect may be observed when co-administered with Paliperidone.

- Co-administration with Carbamazepine decreased mean steady-state Cmax and AUC of Paliperidone by approximately 37%. Adjust dose of Paliperidone if necessary based on clinical assessment.
- Co-administration of Divalproex sodium increased C_{max} and AUC of Paliperidone by approximately 50%. Adjust dose of Paliperidone, if necessary based on clinical assessment.

BRAND NAMES

Invega (Janssen-Cilag, UK)

Palido- OD (Torrent Pharmaceuticals Ltd, India)

Palip- XR (Intas Pharmaceuticals Ltd, India).

(www. drugbank.com, www.fda.gov, www.mims.com)

(Martindale, 36th ed, The complete drug reference)

CHAPTER VII

EXCIPIENTS PROFILE

CHAPTER -VII

EXCIPIENT PROFILE

TWEEN 80

Synonyms

- ✧ Armotan PMO 20
- ✧ Capmul POE-O
- ✧ Cremophor Ps 80
- ✧ Montanox 80
- ✧ Polyoxyethylene 20 oleate

Chemical name

- ✧ Polyoxyethylene 20 sorbitan monooleate

Empirical formula

- ✧ C_{64} H_{24} O_{26}

Molecular weight

- ✧ 1310

Functional Category

- ✧ Emulsifying agent
- ✧ Non ionic surfactant
- ✧ Solubilizing agent
- ✧ Wetting agent
- ✧ Dispersing/ suspending agent

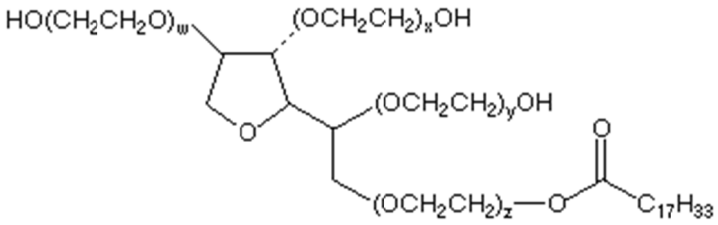
HLB value

- ✧ 15

Viscosity at 25° C

- ✧ 400 mPas

Structural formula



Polysorbate 80
(Sum of w, x, y, and z is 20)

Application in pharmaceutical formulation or technology

- ✧ They may be used as solubilizing agents for a variety of substances including essential oils and oil-soluble vitamins and as wetting agents in the formulation of oral and parenteral suspensions.
- ✧ They have been found to be useful in improving the oral bioavailability of drug molecules.
- ✧ Polysorbates are also widely used in cosmetics and food products.

Description

- ✧ Yellow oily liquid

Melting Point

- ✧ -20.556°C (-5°F)

Solubility

- ✧ Soluble in methanol. Easily soluble in cold water, hot water. Soluble in Toluene, alcohol, cottonseed oil, Ethyl Acetate.
- ✧ Insoluble in mineral oil.

Stability and storage condition

- ✧ Polysorbates are stable to electrolytes and weak acids and bases.
- ✧ Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry place.

Incompatibilities

- ✧ The antimicrobial activity of paraben preservatives is reduced in the presence of polysorbates.

Handling Precautions

- ✧ Observe normal precautions appropriate to the circumstances and quality of material handled. Eye protection and gloves are recommended.

. (Raymond C Rowe., 5th Edition)

PROPYLENE GLYCOL

Synonyms

- ✧ 1,2-Dihydroxypropane
- ✧ 2-hydroxypropanol
- ✧ Methyl ethylene glycol
- ✧ Methyl glycol
- ✧ Propane-1,2-diol

Chemical name

- ✧ 1,2- Propanediol

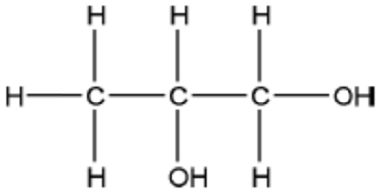
Empirical formula

- ✧ $C_3 H_8 O_2$

Molecular weight

- ✧ 76.09

Structural formula



HLB value

- ✧ 11.6

Functional Category

- ✧ Antimicrobial Preservatives
- ✧ Disinfectant
- ✧ Humectants

- ✧ Plasticizer
- ✧ Solvents
- ✧ Water – Miscible cosolvents

Application in pharmaceutical formulation or technology

- ✧ Propylene glycol has become widely used as a solvent, extractant and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations
- ✧ Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations;
- ✧ Propylene glycol is also used in cosmetics and in the food industry as a carrier for emulsifiers and as a vehicle for flavors in preference to ethanol, since its lack of volatility provides a more uniform flavor.

Description

- ✧ Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling that of glycerin.

Melting Point

- ✧ - 59^{o}C

Solubility

- ✧ Soluble in acetone, chloroform, ethanol, glycerin and water.

Viscosity at 25^{o} C

- ✧ 58.1 mPas

Stability and storage condition

- ✧ Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water.

- ✧ Propylene glycol is hygroscopic and should be stored in a well-closed container, protected from light, in a cool, dry place.

Incompatibilities

- ✧ Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate**.**

Handling Precautions:

- ✧ Propylene glycol should be handled in a well-ventilated environment; eye protection is recommended.

  (Raymond C Rowe., 5th Edition)

POLYETHYLENE GLYCOL 400

Synonym

- ✧ PEG-8

Chemical name

- ✧ Polyethylene Glycol 400

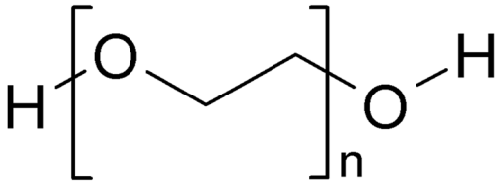
Empirical formula

- ✧ H(OCH2CH2)n OH

Molecular weight

- ✧ 400 (380 - 420) g/mole

Structural formula



Functional Category

- ✧ Ointment base
- ✧ Plasticizer
- ✧ Solvent
- ✧ Tablet and capsule lubricant

Viscosity at 25^{o} C

- ✧ 105- 130 mPas

Application in pharmaceutical formulation or technology

- ✧ Polyethylene glycol is widely used in parenteral, topical, ophthalmic and oral preparations.

Description

- ✧ Clear liquid, odourless.

Melting Point

- ✧ 4°C (39.2°F)

Solubility

- ✧ Soluble in cold water, hot water. Slightly soluble in aliphatic hydrocarbons. Readily soluble in aromatic hydrocarbons.

Stability

- ✧ Stable under ordinary condition, hygroscopic.

Storage

- ✧ Tightly closed container. Keep container in a cool, well-ventilated area.

Precautions

- ✧ Keep away from heat, source of ignition and incompatibles such as oxidizing agents, acids, alkalis.
- ✧ Wear suitable protective clothing.

(www.sciencelab.com and Raymond C Rowe., 5th Edition)

PROPYLENE GLYCOL MONOCAPRYLATE

Synonyms

- ✧ Capryol 90
- ✧ 1,2 propanediol monocaprylate
- ✧ Propylene glycol caprylate
- ✧ Octanoic acid, monoester with 1,2 propanediol

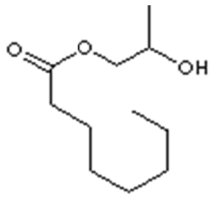
Empirical formula

- ✧ $C_{11}H_{22}O_3$

Molecular weight

- ✧ 202.29

Structural formula



Description

- ✧ Appearance – oily liquid
- ✧ Odour – Faint

Hydrophilic - lipophilic balance: (HLB value)

- ✧ 6

Field of use

- ✧ Human and veterinary products, excluding food producing animals.

Administration Route

- ✧ Oral
- ✧ Topical

Oral: A water insoluble surfactant, used in self emulsifying systems to obtain a coarse dispersion and bioavailability enhancer.

Topical: A water-in-oil surfactant/solubilizer.

Formulation techniques and dosage forms

- ✧ Suitable for soft and hard gelatin capsules.
- ✧ Use in topical ointments, microemulsions and emulsions.

Storage

- ✧ Stable under ordinary condition**.**

Application

- ✧ It is used as a lipophilic emulsifier and emulsion stabilizer in food and personal care products.

  (www.chemicalland21.com)

MICROCRYSTALLINE CELLULOSE

Synonyms

- ✧ Avicel PH
- ✧ Cellet
- ✧ Hellulosum microcristalinum
- ✧ Crystalline cellulose
- ✧ Emcocel

Chemical name

- ✧ Cellulose

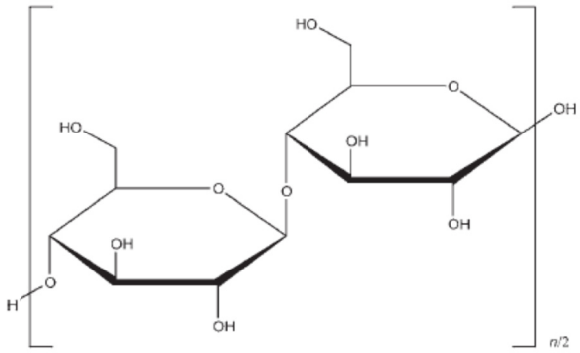
Empirical formula

- ✧ $(C_6 H_{10} O_5)_{220}$

Molecular weight

- ✧ 36000

Structural formula



Functional Category

- ✧ Adsorbent
- ✧ Suspending agent
- ✧ Tablet and capsule diluents

- ✧ Tablet disintegrant

Application in pharmaceutical formulation or technology

- ✧ Microcrystalline cellulose is widely used in pharmaceuticals primarily as binder/diluents in oral tablet and capsule formulation.
- ✧ It is used as binder/diluents.
- ✧ Microcrystalline cellulose is also used in cosmetics and food products.

Description

- ✧ Microcrystalline cellulose is a white, odorless, tasteless, crystalline powder composed of porous particles.

.**Melting Point**

- ✧ 260-270^{o}C

Solubility

- ✧ Slightly soluble in 5% w/v NaOH solution, practically insoluble in water and most organic solvents.

Stability and storage condition

- ✧ Microcrystalline cellulose is stable though hygroscopic material.
- ✧ It should be stored in a well-closed container in a cool, dry place.

Incompatibilities

- ✧ Microcrystalline cellulose is incompatible with strong oxidizing agent.

Handling Precautions

- ✧ Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection and dust mask are recommended.

(Raymond C Rowe., 5th Edition)

SILICA

Synonyms

- ✧ Aerosil
- ✧ Cab-O-sil
- ✧ Colloidal silica
- ✧ Fumed silica
- ✧ Fumed silicon dioxide
- ✧ Silicone dioxide colloidal

Chemical name

- ✧ Silicon dioxide

Empirical formula

- ✧ SiO_2

Molecular weight

- ✧ 60.08

Functional Category

- ✧ Adsorbent
- ✧ Anticaking agent
- ✧ Glidant and Tablet disintegrant
- ✧ Emulsion stabilizer
- ✧ Viscosity increasing agent

Application in pharmaceutical formulation or technology

- ✧ It is improves the flow properties of the dry powders.
- ✧ It is used as an adsorbent dispersing agent for liquids in powders.
- ✧ Eliminate hard settling and minimize the clogging of spray nozzle.

Description

- ✧ Colloidal silicone dioxide is a light, loose, bluish-white coloured, tasteless, odorless and amorphous powder**.**

Melting Point

- ✧ 1600^{o}C

Solubility

- ✧ Soluble in hot solution of alkali hydroxide. Practically insoluble in water, organic solvents and acids.

Storage condition

- ✧ It should be stored in a well closed container.

Incompatibilities

- ✧ It is incompatibility with diethylstilbestrol preparations.

Handling Precautions

- ✧ A dust mask should be used, when handling small quantity. For large quantities, a dust respirator is recommended.

  (www.chemicallab.com and Raymond C Rowe., 5th Edition)

SODIUM STARCH GLYCOLATE

Synonyms

- ✧ Carboxy methyl starch, sodium salt
- ✧ Explotab
- ✧ Glycolys
- ✧ Starch carboxymethyl ether
- ✧ Explosol

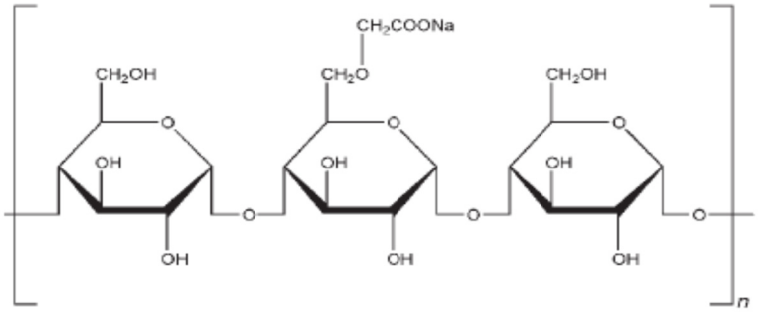
Chemical name

- ✧ Sodium carboxymethyl cellulose

Molecular weight

- ✧ Estimated 500,000 - 1,000,000

Structural formula



Functional Category

- ✧ Tablet and capsule disintegrant.

Application in pharmaceutical formulation or technology

- ✧ Sodium starch glycolate is used as a disintegrant in tablet and capsule formlation.Rapidly disintegration of tablets occurs.

Description

- ✧ White, free flowing hygroscopic powder.

Melting Point

- ✧ Does not melt, but chars at approximately 200^{o}C.

Solubility

- ✧ Practically insoluble in methylene chloride

Storage condition

- ✧ It should be stored in a well closed container in order to protect it from temperature and humidity.

Incompatibilities

- ✧ Sodium starch glycolate is incompatible with ascorbic acid

Handling Precautions

- ✧ Eye protection, gloves, dust mask or respirator is recommended.

(Raymond C Rowe., 5th Edition)

MAGNESIUM STEARATE

Synonyms:

- ✧ Magnesium distearate
- ✧ Dibasic magnesium stearate
- ✧ Octadecanoic acid, magnesium salts
- ✧ Magnesium octadecanoate

Chemical name

- ✧ Octadecanoic acid magnesium salt

Empirical formula

- ✧ $C_{36}H_{70}MgO_4$

Molecular weight

- ✧ 591.24

Structural formula

- ✧ $[CH(CH_2)_{16}COO]_2Mg$

Functional Category

- ✧ Tablet and capsule lubricant.

Application in pharmaceutical formulation or technology

- ✧ It is used as a lubricant in tablet and capsule formulation.
- ✧ It is widely used in foods, cosmetics and pharmaceutical formulations.

Description

- ✧ Magnesium stearate is a very fine, light white.
- ✧ The powder is greasy to the touch and readily adheres to the skin.

Melting Point

- ✧ 117-150^{o}C

Solubility

- ✧ Slightly soluble in warm benzene and warm ethanol.
- ✧ Practically insoluble in ethanol and water.

Storage condition

- ✧ It should be stored in a well-closed container in a cool and dry place.

Incompatibilities

- ✧ Incompatible with strong acids, alkalis and iron salts.
- ✧ Magnesium stearate cannot be used in product containing aspirin and some vitamins.

Handling Precautions

- ✧ Eye protection and gloves recommended.

  Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended

  (Raymond C Rowe., 5th Edition).

TALC

Synonyms

- ✧ Altalc
- ✧ E553b
- ✧ Hydrous magnesium silicate
- ✧ Purified French chalk
- ✧ Purtalc

Chemical name

- ✧ Talc

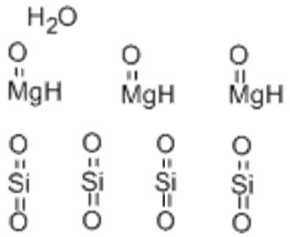
Empirical formula

- ✧ $Mg_6 (Si_2O_5)_4 (OH)_4$

Molecular weight

- ✧ 379.27

Structural formula



Functional Category

- ✧ It is used as a diluents and lubricant in a tablet and capsule formulations.
- ✧ Anticaking agent

Application in pharmaceutical formulation or technology

- ✧ It is widely used as a dissolution retardant in the development of controlled-release products.
- ✧ It is used as a diluents and lubricant in oral solid dosage formulations.

Description

- ✧ Talc is a very fine, white to grayish – white, odorless.
- ✧ It adheres readily to the skin and is soft to the touch and free from grittiness.

Melting Point

- ✧ 800^{o}C

Solubility

- ✧ Practically insoluble in organic solvents, water and in dilute acids & alkalis.

Stability and storage condition

- ✧ Talc is stable material and may be sterilized by heat in at 160^{o}C for not less than one hour and also sterilized by exposure to ethylene oxide or gamma irradiation.
- ✧ It should be stored in a well-closed container in a cool and dry place.

Incompatibilities

- ✧ Incompatible with quaternary ammonium compounds.

Handling Precautions

- ✧ Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis.
- ✧ Eye protection, gloves and respirator is recommended.

(Raymond C Rowe., 5th Edition)

CHAPTER VIII

EXPERIMENTAL DETAILS

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1. PREPARATION OF STANDARD CALIBRATION CURVE

a) Determination of λ_{max}

A known weight (100 mg) of drug (Paliperidone) is dissolved in 25ml of methanol and diluted to 100ml using a distilled water to form a primary stock solution (1000µg/ml). The stock solution is further diluted using distilled water to 10µg/ml concentration. The resultant solution is scanned in the range of (200-400nm) by Ultra visible Spectrophotometer (UV-1700 Shimadzu corporation, Japan) to get absorption maximum (λ_{max}) (Anuja Pandey *et al*., 2013 and Vinay Kumar *et al*., 2012).

b) Preparation of Calibration Curve

From the above prepared stock solution, different concentration (1 to 10µg/ml) solutions are prepared using distilled water. The absorbances of these solutions are measured at λ_{max} (237nm) by UV- spectrophotometer (UV-1700 Shimadzu Corporation, Japan). A standard curve is plotted using concentration on X-axis and the absorbance obtained on Y-axis.

2. SOLUBILITY STUDIES:

Solubility studies of Paliperidone is carried out in Propylene glycol, Polyethylene glycol 400 (PEG 400), Tween 80, Capryol 90 and in distilled water. Saturated solutions are prepared by adding excess drug to the vehicles and shaking on the shaker for 48 hours at 25 ± 0.5 ^{0}C under constant vibration. After this period the solutions are filtered, diluted and analysed by UV Spectrophotometer. Three determinations are carried out for each sample to calculate the solubility of Paliperidone (Jabbar *et al*., 2013).

3. PREFORMULATION (COMPATIBILITY) STUDIES

The compatibility studies are carried out by infrared spectroscopic studies (IR) in order to evaluate the drug and polymer interaction.

a) Infrared spectroscopic Studies

Infrared spectra of pure drug, carrier and coating materials are obtained with a Shimadzu, Japan. Samples are prepared in KBr disks (2mg sample in 200mg KBr). The scanning range is 4000 to 400 cm^{-1} (Vinay kumar *et al*., 2012).

4. FLOWABLE LIQUID-RETENTION POTENTIAL (Φ-VALUE) OF THE EXCIPIENTS (AVICEL PH 102 AND AEROSIL 200)

a) Determination of the angle of slide

The Angle of slide for carrier and coating material (10 gm of Avicel PH 102 and Aerosil 200) is measured as follows:

The excipients are weighed accurately and placed at one end of a metal plate with a polished surface. This end is raised gradually until the plate made an angle with the horizontal at which as a measure for the flow characters of powders. An angle of slide θ corresponding to 33°corresponded to optimal flow properties (Shah *et al*., 2012, A. A. Elkordy *et al*., 2012 and Dina Louis *et al*., 2008).

b) Determination of flowable liquid-retention potential (φ-value)

To the 10 g of excipients, increasing amounts of liquid vehicle are added and mixed well. The excipients adsorbed liquid vehicle resulting in a change in its flow properties. At each concentration of liquid vehicle added, the angle of slide θ for excipients are re-determined as stated above. The corresponding Φ-value is calculated from the following equation.

Φ-value = weight of liquid/weight of solid

The Φ-values are plotted graphically against the corresponding angles of slide (h). The Φ-value corresponding to an angle of slide of 33° represented the flowable liquid-retention potential of excipients.

The Φ-value for Avicel PH 102 and Aerosil 200 is reported in the table below and hence there is no need to determine it practically (Amal Ali Elkordy *et al*., 2013 and Dina Louis *et al*., 2008)

Table 3: Φ–values for carrier material and coating material

(Spireas *et al*., 1998 and Abdul Hasan Sathali A. and Deepa C. *et al*., 2013)

Non-Volatile liquid Vehicles	**Φ-value for carrier material (Avicel PH102)**	**Φ-value for coating material (Aerosil 200)**
1.Propylene glycol	0.16	3.31
2.polyethylene glycol400	0.005	3.26
3.Tween 80	0.003	3.95
4.Cremophor EL	0.18	0.80
5.capryol 90	0.16	0.40

These values are used for the preparation of liquisolid tablets.

5. PROCEDURE FOR PREPARATION OF LIQUISOLID SYSTEM

Several Paliperidone liquisolid formulations are prepared in batches of 60 tablets at different ratios of (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10) drug: liquid vehicles. Each formulation contains Avicel PH102 as carrier and Aerosil 200 as coating material, at carrier/coat ratio(R value) of 20 and 30. The appropriate amounts of carrier and coating materials used for each formulation depend upon Lf of that formulation. The ΦCa and ΦC_0 values for each particular liquid vehicle are used to calculate Lf [Eq- (1)] of that respective liquid vehicle. Once the liquid load factor (Lf)

and amount of liquid medication (W) are determined amount of carrier (Q) and coating (q) can be calculated by rearranging Eq- (2) and (3)

$$Lf = \Phi Ca + \Phi C_0 \times 1/R \quad \text{——————} \quad (1)$$

$$Lf = W/Q \quad \text{——————} \quad (2)$$

$$R = Q/q \quad \text{——————} \quad (3)$$

The drug-vehicle liquid system is produced by mixing Paliperidone (6mg/ tablet) in non-volatile liquid vehicle using a mortar and pestle. To this liquid medication, the calculated amount of the carrier (Avicel PH102) is added by continuous mixing in the mortar. Then the coating material (Aerosil 200) is carefully added and mixed until mortar contents start to look like dry powder. In the last stage of the preparation, a 5% (w/w) sodium starch glycolate as a super disintegrant and 0.75% (w/w) of magnesium stearate as a lubricant are added and mixed. All liquisolid preparations are compacted into tablets using a single punch tablet machine (Cadmah, Mumbai) having 10mm flat punch. The applied compression force is different from one formulation to another formulation depending on the weight of the tablet and the preparation (Dinesh M. Pardhi *et al*., 2010 and Spiro Spireas *et al*., 1998).

6. PREPARATION OF DIRECTLY COMPRESSED TABLETS

For comparison conventional Paliperidone (6mg/tablet) are prepared by mixing all tablet excipients, except non-volatile liquid vehicle compressed into tablets (Amal Ali Elkordy *et al*., 2012 and Spiro Spireas et *al*., 1998).

Table 4: Composition of directly compressed tablets

S. No	Ingredients	Quantity for one tablet (mg)
1.	Paliperidone	6
2.	Avicel PH102	490.09
3.	Aerosil 200	16.33
4.	Sodium starch glycolate	25.62
5.	Magnesium stearate	4.03

Total Weight = 542.07mg

7. PRECOMPRESSIONAL EVALUATION OF POWDER BLEND

a) Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. In this method, a fixed funnel method procedure is performed in triplicate and average angle of repose calculated (Kamalakanan V. *et al*., 2012 and Aulton M.E., 2002).

$$\tan \theta = h/r$$

Where,

θ = angle of repose

h = height of pile

r = radius of pile

The relationship between the angle of repose and powder flow is as follow in the table:

Table 5: Limits for angle of repose

ANGLE OF REPOSE	POWDER FLOW
$< 25^o$	Excellent
$25\text{-}30^o$	Good
$30\text{-}40^o$	Passable
$>40^o$	Very poor

b) Bulk density

Bulk density is the ratio between given mass of powder and its bulk volume. Bulk density is carried out in triplicate. Bulk density measurements are carried by placing fixed weight of powder in graduated cylinder and volume occupied is measured and initial bulk density is calculated. It is expressed in gm/ml. Bulk density is calculated by using following formula (Kamalakanan V. *et al*., 2012 and Pradeep Yala *et al*., 2012)

$$\text{Bulk Density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of the powder}}$$

c) True density

True density is the ratio between given mass of powder and constant volume of powder after tapping. True density measurements are carried by cylinder is then tapped at a constant velocity till a constant volume is obtained. Then tapped density is calculated by using following formula (Kamalakanan V. *et al*., 2012 and Pradeep Yala *et al*., 2012)

$$\text{True Density} = \frac{\text{Mass of the powder}}{\text{Tapped volume of the powder}}$$

d) Carr's Index

Flowability is assessed from Carr's compressibility Index (CI %). The CI is calculated from the poured (bulk density) and tapped densities. Tapped density is measured by tapping fixed weight of the sample into 100 ml measuring cylinder several times using a tap density apparatus till a constant volume is obtained, where the powder is considered to reach to its most stable arrangement. Carr's compressibility index is then calculated using the following Equation (Devendra Revanand Rane et al., 2012 and Aulton M.E., 2002)

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

The smaller the value of the CI%, the superior the flow properties of the powder

Table 6: Values of Carr's Index

CARR'S INDEX	TYPE OF FLOW
5 – 15 %	Excellent
15 -25 %	Good
>25 %	Poor

e) Hausner's Ratio

Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property. It is calculated by the following formula

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Values less than 1.25 indicate good flow (=20% carr), and greater than 1.25 indicates poor flow (=33% carr). Between 1.25 and 1.5, added glidant normally improves flow (Devendra Revanand Rane *et al*., 2012 and Aulton M.E., 2002).

f) Drug content

The Powder blend containing 10 mg equivalent of drug weighed and dissolved in methanol, then the volume is made upto 100ml with distilled water. From the above solution, 10 ml is taken and diluted with distilled water. The absorbance of resulting solution is measured at 237 nm using UV spectrophotometer (Shimadzu UV-1700 pharma spec, Japan) and the drug content is estimated.

8. POSTCOMPRESSIONAL EVALUATION OF LIQUISOLID TABLETS

a) General appearance

The formulated tablets are evaluated for general appearance such as colour, shape and appearance (Prasanth Sai R.V *et al*., 2011).

b) Thickness

Three tablets are randomly selected from each formulations and thickness is measured individually by vernier caliper. It is expressed in millimeter (mm) and average is calculated (Amit modi *et al*., 2012).

c) Hardness

Tablet requires a certain amount of hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packing and shipping. The hardness of the tablets is determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Three tablets are randomly selected from each formulation and hardness of the tablets is determined. The results are expressed in average value (Dnyanesh walunj *et al*., 2012).

d) Weight variation

Twenty tablets are randomly selected from each formulation and average is determined. Then individual tablet are weighed and individual is compared with average weight. The tablet pass the USP test if no more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit (Sanjeev Raghavendra Gubbi et al., 2010)

Table 7: Limits for weight variation test

AVERAGE WEIGHT	MAXIMUM % DIFFERENCE ALLOWED
130 mg or less	± 10 %
130 mg to 324 mg	± 7.5 %
More than 324 mg	± 5 %

e) Friability test

The friability of tablets is determined using Roche friabilator. Twenty tablets are randomly selected from each formulation and initial weight of 20 tablets are calculated and then transferred into friabilator. The friabilator is operated at 25 rpm for 4 minutes (100 revolutions). The tablets are dedusted and weighed again (final weight). The percentage friability is calculated by the following equation

$$F = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Compress tablet that lose less than 0.1 to 0.8% of the tablet weight are consider acceptable (Anand Kishore *et al*., 2011).

f) Drug content

The total amount of drug present in the liquisolid formulation is evaluated using UV-spectrophotometric analysis. Approximately weighed quantity of 10mg equivalent of drug is taken from liquisolid formulation which is dissolved in 10ml of methanol and the volume is made upto 100ml with distilled water. From the above solution, 10 ml is taken and diluted with distilled water. The absorbance of resulting solution (10µg/ml) is measured at 237 nm using spectrophotometer (shimadzu UV-1700 pharma spec, Japan) and the drug content is calculated from the standard curve using the formula (Srinivas Vaskula *et al*., 2012).

$$\text{Drug content} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times 100$$

g) Disintegration test

Disintegration is defined as that state in which no residue of the tablet or capsule remains on the screen of the apparatus. The disintegration time of the liquisolid tablets is determined using disintegration test apparatus. Introduce one tablet into each tube and floating of the tablets can be prevented by placing a perforated plastic disc to each tube. Suspend the basket rack in the beaker containing the 900 ml of distilled water at 37□ C and move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28-32 cycles per minutes and the disintegration time for each formulations is noted (Indian Pharmacopoeia., 1996. Page no: A-80 to A-81).

Disintegration time

a) Uncoated tablets: 5- 30 minutes
b) Coated tablets: 1-2 hours

9. *IN VITRO* RELEASE STUDIES

In vitro release studies is performed by using USP type II Paddle dissolution apparatus in 900 ml of distilled water maintained at 37° C ± 0.5° C and rotation speed of 50 rpm. Samples (5 ml) are withdrawn at suitable time intervals (5, 10, 15, 20, 25, 30, 45, 60 minutes) and filtered through whatman filter paper. Sink conditions are maintained throughout the study. The withdrawn samples are analyzed by UV-visible spectrophotometer (Shimadzu UV-1700 pharma spec, Japan) at λ_{max} of 237nm. The studies are done in triplicate (Dinesh M. Pardhi *et al*., 2010 and www.fda.gov).

10. POWDER X-RAY DIFFRACTION STUDIES

Powder X-ray diffraction pattern of Paliperidone, Avicel PH102, Aerosil 200 and liquisolid formulation (Best formulation) are studied using X-ray diffractometer (XRD-462, Digaku, Japan) with CuKα radiation. Voltage and current are set 40 kV and 30 mA respectively. All pattern scanned over range 5-70^{o} 2θ angle with a scan speed of 10^{o}/min (Hirokazu Matsunaga *et al*., 1999).

11. ASSESSMENT AND COMPARISON OF DRUG DISSOLUTION RATES

The dissolution rate of Paliperidone is the amount of drug (in µg) dissolved per minute by each tablet formulation during first 10 min is calculated by the following equation (Shashidher Burra *et al*., 2011 and Nokhodchi A *et al*., 2005)

$$D_R = \frac{(M \times D)}{1000}$$

Where,

M = Total amount of pure drug in each tablet (in µg)

D = Percentage of drug dissolved in the first 10 minutes

12. SELECTION AND EVALUATION OF BEST FORMULATION

The best formulation is selected depending on the results obtained from solubility studies in various non-volatile liquid vehicles and *in vitro* release studies.

a) Comparison with directly compressed tablets

The *in vitro* release of best formulation is compared with directly compressed tablets are prepared by mixing all tablet excipients, except non-volatile liquid vehicle (Amal Ali Elkordy *et al*., 2012 and Spiro Spireas et *al*., 1998).

b) Infrared spectroscopic studies for best formulation

Liquisolid formulation (Best formulation) is subjected to infrared Spectroscopic studies as per the procedure already discussed in compatibility studies.

c) Differential Scanning Colorimetric (DSC) studies for best formulation

Thermal curves of pure drug, carrier, coating material and liquisolid formulation (Best formulation) are recorded by simultaneous differential scanning calorimeter (DSC Q200 V24.4 Build 116). Each sample (approximately 2.5mg) are scanned in hermetic pan made of aluminium at heating rate of 10° C / min over the range of 50° C - 220° C with an empty aluminium pan used as reference. Samples are heated under nitrogen atmosphere (flow rate of N2 – 50 ml / min) (Anuja pandey *et al*., 2013 and Abdul Hasan Sathali A. and Gopinath M. *et al*., 2013).

d) SEM analysis for best formulation

SEM is used to assess the morphological characteristics of the final liquisolid compacts. The samples are fixed on aluminium stubs with double-sided tape, gold coated sputter examined in the microscope using an accelerating voltage of 15 KV, at a working distance of 8 mm and magnification of X10000 (Pradeep Yala *et al*., 2012).

e) Stability studies

The best formulation of three batches is stored at 40° C ± 2°C and relative RH 75% ± 5% for two months. The best formulation is evaluated using dissolution test, drug content, physical appearance, hardness and thickness. The above tests of best formulations are compared with those of freshly prepared tablets (Prasanth Sai R.V *et al*., 2011 and Amit Modi *et al*., 2012).

CHAPTER IX

RESULTS AND DISCUSSION

CHAPTER - IX

RESULTS AND DISCUSSION

1. PREPARATION OF STANDARD CALIBRATION CURVE

The λ_{max} of paliperidone was determined by scanning the (10µg/ml) solution of drug in distilled water by UV-spectrophotometer and it was found to be 237 nm (Anuja pandey *et al*., 2013 and Pandey A *et al*., 2013) **(Figure 4)**. The absorbance of the solution (1-10 µg/ml) was measured in UV-spectrophotometer at 237 nm. The linear correlation coefficient was found to be $\gamma = 0.9998$. The results were shown in **Table 8** and the calibration graph of paliperidone was shown in **Figure 5**.

2. SOLUBILITY STUDIES

The solubility of paliperidone was determined in various non-volatile liquid vehicles such as Propylene glycol (PG), Polyethylene glycol (PEG 400), Tween 80, Capryol 90 and in distilled water shown in **Table 9** and **Figure 6**. From the results, it was observed that the solubility of drug in Tween 80 was higher when compared with other liquid vehicles which may be due to the high viscosity and HLB value (Pande V. V et al ., 2013).

3. PREFORMULATION (COMPATIBILITY) STUDIES

a) Infrared Spectroscopic Studies

Infrared (IR) spectroscopic studies were carried out to confirm the compatibility between drug and excipients used for the preparation of liquisolid tablets. The IR studies were performed for paliperidone (pure drug), non-volatile liquid vehicle, microcrystalline cellulose, aerosil 200 and physical mixture of drug and excipients. The spectra studied at 4000cm^{-1} to 400 cm^{-1} were shown in **Figure 7a to 7e**.

The principal peaks for pure drug were observed at wave numbers 3294.79 cm^{-1}, 2934.94 cm^{-1}, 1630.56 cm^{-1}, 1534.61 cm^{-1}, 1445.03 cm^{-1}, 1338.91 cm^{-1}, 1271.49 cm^{-1}, 1129.66 cm^{-1}, 956.84 cm^{-1}, 867.3 cm^{-1}.

Further in the physical mixtures, all the above characteristics peaks of the drug appear in the spectrum, which indicated that there was no interaction between the drug and polymers in the physical mixture.

4. FLOWABLE LIQUID-RETENTION POTENTIAL (Φ-VALUE) FOR EXCIPIENTS

Angle of slide was used to determine the Φ-value for the excipients (which are needed for calculation of the L_f). The Φ_{CA}-value (carrier) and Φ_{CO}-value (coating material) decided the appropriate quantities of carrier and coating materials required to convert a given amount of liquid medication into a dry-looking, free flowing and readily compressible liquisolid formulation. Flowable liquid-retention potential values for excipients were taken from literature (Spireas *et al*., 1998)

The flowable liquid-retention potential (Φ-value) for Avicel PH102 (carrier) in Tween 80 was approximately 0.003.

The flowable liquid-retention potential (Φ-value) for Aerosil 200 (coating material) in Tween 80 was approximately 3.95.

The relatively high Φ -value is advantageous as it results in smaller sizes of the tablets. The above values were used to formulate liquisolid tablets of Paliperidone (Amal Ali Elkordy *et al*., 2013).

5. PROCEDURE FOR PREPARATION OF LIQUISOLID POWDER

Liquisolid powder of paliperidone were prepared using non-volatile liquid vehicle Tween 80 at different ratios of (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10) drug: liquid vehicles. The microcrystalline cellulose (Avicel PH102) was used as a

carrier and silica (Aerosil 200) as coating material. Finally 5% (w/w) sodium starch glycolate as a super disintegrant and 0.75% (w/w) of magnesium stearate as a lubricant were added and mixed. All liquisolid preparations were compacted into tablets using a single punch tablet machine (Cadmah, Mumbai) having 10mm flat punch. The compositions of all the formulations were given in **Table 10A and 10B**. Twenty formulations (F1- F20) were prepared.

6. PREPARATION OF DIRECTLY COMPRESSED TABLETS

A conventional formulation of paliperidone were prepared by using drug (Paliperidone), Microcrystalline cellulose (Avicel PH 102), Silica (Aerosil 200) and sodium starch glycolate, without addition of any non-volatile liquid vehicles. The composition of the formulation was given in **Table 10C.**

7. PRECOMPRESSIONAL EVALUATION OF POWDER BLEND

Powder flow is a critical character that might affect uniformity of the tablet weight. Therefore, the flow properties of the powder blend of all liquisolid formulations were determined in order to calculate that the amount of carrier and coating materials were required to maintain acceptable flow and compaction properties. The powder blend of all formulations was evaluated for precompression parameters such as angle of repose, bulk density, true density, carr's index, Hausner's ratio and drug content.

a) Angle of Repose

The angle of repose is a characteristic of the internal friction or cohesion of the particles, the value will be low, if the powder is non-cohesive and high if the powder is cohesive. All the prepared formulations were in the ranges from 24.70^{o} to 29.39^{o}, which indicates the good flow properties of liquisolid powder. The results of angle of repose of all formulations were shown in **Table 11** and **Figure 9a.**

b) Bulk density

Bulk density was used to measure the flow properties of the powder. The bulk density of the powder blend was in the range of 0.206 gm/ml to 0.825 gm/ml. The results of bulk density for all the formulations were shown in **Table 11** and **Figure 9b**.

c) Tapped density

The tapped density of the powder blend was in the range of 0.250 gm/ml to 0.967 gm/ml. The results of bulk density for all the formulations were shown in **Table 11** and **Figure 9c.**

d) Carr's Index (CI)

Determination of carr's index, the ratio of bulk and tapped density, was used to measure the flow property of all liquisolid formulations. The decrease the value of the CI% would indicate the better flow properties of the powder. The carr's index of the all formulations was found to be in range of 6.41% to 19.99%. It was less than 25%, which indicates that the powder blend have required flow property for compression of tablets. The results of carr's index of all formulations were shown in **Table 11 and Figure 9d.**

e) Hausner's Ratio

The Hausner's ratio of all the formulations was found to be in range of 1.06 to 1.24, which indicates better flow property of the powder blend. The results were shown in **Table 11** and **Figure 9e.**

f) Drug content

The percentage drug content for all formulations was found to be in the range of 97.90% to 99.64%, ensured the uniformity of the drug content. The results

indicated all the formulations were within the limits as per IP (Limit: not less than 85% and not more than 115%). The results were shown in **Table 12** and **Figure 9f**.

All the above precompressional evaluations were done for directly compressed tablets and they were within the limit (**Table 15A**).

8. POSTCOMPRESSIONAL EVALUATION OF LIQUISOLID TABLETS

Tablets of different formulations were evaluated for the postcompressional parameters such as general appearance, weight variation, hardness, thickness, friability, disintegration time and drug content for tablets.

a) General appearance

The formulated tablets were white in colour, biconvex and round shape. All the tablets were elegant in appearance. The results were shown in the **Table 13.**

b) Thickness

The thickness of all the tablet formulations was used to determine the uniformity of size and shape of the tablets. All the prepared tablet formulations were measured by vernier caliper and were found to be in the range of 2.45 to 5.2mm. The results indicated that all the formulations had uniform size and shape. The results were shown in **Table 13.**

c) Hardness

Hardness of tablet was used to determine the resistance to withstand mechanical shakes of handling in manufacture and packing. All the prepared tablets were determined using Monsanto hardness tester. The hardness of all the formulations was found to be 4 to 5 Kg/cm^2, which indicates that all the tablet formulations had good mechanical strength. The results of all the formulations were shown in **Table 13.**

d) Weight variation

The weight variation was used to ensure the uniformity of the tablet in all formulations. All the formulated tablets passes the weight variations within the acceptable limits as per IP. The results were shown in the **Table 13.**

e) Friability test

The friability of tablets was determined using Roche friabilator and used to determine the mechanical strength of tablets. The percentage friability of all the tablet formulations was found to be in the range of 0.10 to 0.77 %. It was less than 1%; the results indicated that all the tablet formulation had a good mechanical resistance of tablets. The results were shown in **Table 13.**

f) Drug content

The drug content was used to determine the uniform amount of active ingredients present in all the formulations. The drug content was found to be in the range of 99.18% to 99.99%, which indicates all the formulations were within the acceptable limits as per IP (Limit: not less than 85% and not more than 115%). The results were shown in **Table 14.**

g) Disintegration test

The disintegration time of all the tablet formulations was determined using Disintegration test apparatus. All the prepared tablet formulations were in between 3 min 30 sec to 8 min 7 sec. It was lesser than 15 min, which indicates all the formulations were within the acceptable limits as per IP. The results were shown in **Table 13.**

All the above postcompressional evaluations were done for directly compressed tablets and they were within the limit **(Table 15B).**

9. *INVITRO* RELEASE STUDIES

In vitro dissolution studies were carried out by USP type II method by using distilled water as a medium. The studies were performed in all the formulations for 1 hour. The samples were taken at 5min interval for first 30 minutes, 15mins interval for next 30 minutes and absorbance was measured in UV spectrophotometer at 237nm.

Two formulation parameters such as effect of drug concentration in the liquid medication (ratio of drug and liquid vehicle) and effect of carrier/coating ratio (R-value) that would affect the drug dissolution rate in immediate release liquisolid tablets were investigated.

The results of *in vitro* release studies from liquisolid formulations shown in **Table 16A to 16D** and **Figure: 10a to 10e.**

Formulations F1, F3, F5, F7, F9, F11, F13, F15, F17 and F19 were prepared with 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9 and 1:10 (ratio of drug and Tween 80) and 20:1 (ratio of MCC & Aerosil 200) showed the cumulative % of drug release 64.11%, 68.03%, 73.20%, 76.50%, 80.43%, 83.09%, 88.52%, 93.08%, 95.48%, and 94.24% respectively at the end of 1 hour. Among the ten formulations F17 showed maximum release of 95.48%. The orders of percentage drug release were

F1<F3< F5<F7<F9<F11<F13<F15<F19<F17

Formulations F2, F4, F6, F8, F10, F12, F14, F16, F18 and F20 were prepared with 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9 and 1:10 (ratio of drug and Tween 80) and 30:1 (ratio of MCC & Aerosil 200) showed the cumulative % of drug release 65.24%, 70.63%, 74.75%, 79.13%, 84.95%, 85.71%, 90.28%, 96.79%, 98.10% and 99.24% respectively at the end of 1 hour. Among the ten formulations F20 showed maximum release of 99.24%. The orders of percentage drug release were

F2<F4< F6<F8<F10<F12<F14<F16<F18<F20

The formulations prepared with higher ratio of drug: liquid vehicle (1:10) have higher dissolution than smaller ratio of drug: liquid vehicle (1:1) in liquisolid formulations.

From the above results, it was observed that the drug release was faster for formulation F20, containing the ratio 1:10 (drug:Tween 80) due to increase the amount of liquid vehicles. The enhanced drug dissolution rate may be mainly attributed to the fact that this poorly water-soluble drug is already in solution in Tween 80, while at the same time, it is carried by the powder particles (microcrystalline cellulose-silica) of liquid vehicle. Thus, its release is accelerated due to its markedly increased wettability and surface availability to the dissolution medium.

Microcrystalline cellulose and Aerosil 200 were used as carrier and coating materials, respectively in prepared formulations. The effect of carrier and coating material ratio (R-value) on the drug dissolution were investigated. Two R-value of 20 and 30 were studied. Generally, the higher R-value showed higher drug dissolution than the lower R-value.

It was observed that formulation F20 with higher R-value showed a higher drug release than the formulation with lower R-value. Liquisolid tablets with high R-value would contain high amount of microcrystalline cellulose (act as disintegrant), low amount of Aerosil 200 (hydrophobic in nature that would retard drug release) and low liquid load factor.

The overall results indicated that the prepared immediate release liquisolid tablet formulation (F20) at the ratio of 1:10 (drug: Tween 80) and the higher R-value (30) which improved the dissolution behavior of drug (Nokhodchi. A *et al*., 2005).

Among all the 20 formulations, F20 was selected as a best formulation which had the better drug release rate (99.24% at 1hour). Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability.

10. POWDER X-RAY DIFFRACTION STUDIES

Polymorphic changes in the drug are important factor which might affect the dissolution rate of drug and in turn bioavailability. So that it is necessary to study the polymorphic changes of pure drug in liquisolid systems. The crystalline nature of drug was studied by the characteristic PXRD pattern which showed sharp peaks at 14.81°, 21.40°, 22.00°, 23.17°, 24.80° and 26.40° at 2θ. PXRD for pure drug, excipients and liquisolid systems were showed in **Figure 11a to 11d.**

Avicel PH 102 has a sharp characteristic peak at 22.78 at 2θ while liquisolid formulation powder obtained only one sharp characteristic peak at 23.00 at 2θ, which is evidence that Avicel PH 102 maintained its crystalline state. Liquisolid powder x-ray diffraction pattern showed absence of these characteristic peaks of drug, which indicated pure drug, was entirely converted into amorphous or solubilized from. The absence of crystalinity in the liquisolid formulation might be due to solubilization of drug in liquid vehicle that is possibly absorbed and adsorbed on the carrier and coating material. The amorphization or solubilization of pure drug may result in an enhancement of dissolution rate (Sanjeev Ragavendra Gubbi *et al*., 2010 and Abdul Hasan Sathali A. and Deepa C. *et al*., 2013).

11. ASSESSMENT AND COMPARISON OF DRUG DISSOLUTION RATES

The concentration of drug and Tween 80 is one of the main factors for the formulation of a liquisolid tablets and has considerable effect on the 10 min dissolution rate. Dissolution rate increased with an increase in the concentration of

Tween 80 due to high molecular dispersion states of the drug in the formulations. The results were shown in **Table 17.** The comparison of dissolution rate for pure drug, directly compressed tablets and liquisolid formulation were shown in **Table 18** and **Figure 12.**

Formulations F1, F3, F5, F7, F9, F11, F13, F15, F17 and F19 were prepared with 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9 and 1:10 (ratio of drug and Tween 80) and R-value of 20 showed the dissolution rate of 80.70 µg/min, 103.49 µg/min, 125.00 µg/min, 150.32 µg/min, 176.90 µg/min, 198.42 µg/min, 216.14 µg/min, 232.60 µg/min, 252.85 µg/min and 255.38 µg/min respectively at 10 min. Among the ten formulations F19 showed maximum dissolution rate of 255.38 µg/min.

Formulations F2, F4, F6, F8, F10, F12, F14, F16, F18 and F20 were prepared with 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9 and 1:10 (ratio of drug and Tween 80) and R-value of 30 showed the dissolution rate of 100.95 µg/min, 119.94 µg/min, 135.13 µg/min, 156.65 µg/min, 188.29 µg/min, 206.02 µg/min, 231.33 µg/min, 256.56 µg/min, 268.04 µg/min and 281.96 µg/min respectively at 10 min. Among the ten formulations F20 showed maximum dissolution rate of 281.96 µg/min.

From the above results, it was observed that the dissolution rate was higher for formulation F20, containing the ratio 1:10 (drug:Tween 80).

The dissolution rate of pure drug, directly compressed tablet and liquisolid formulation were showed 33.87 µg/min, 71.84µg/min and 281.96 µg/min respectively. As it clear from the figure 12, the liquisolid tablets displayed higher dissolution rate than those of directly compressed tablet and pure drug.

According to the classic dissolution equation:

$$D_R = (D/h)\, S\, (C_S - C)$$

The drug dissolution rate (D_R) of a drug is directly proportional to its concentration gradient ($Cs–C$) in the stagnant diffusion layer and its surface (S) available for dissolution. Cs is the saturation solubility of the drug in the dissolution medium and, thus, it is a constant characteristic property related to the drug and dissolving liquid involved. Since all of dissolution tests for formulations were done at a constant rotational paddle speed (50 rpm) and identical dissolving media, we can assume that the thickness (h) of the stagnant diffusion layer and the diffusion coefficient (D) of the drug molecules remain almost identical. Therefore, the observed higher dissolution rates of paliperidone from liquisolid tablets are due to the significantly increased surface of the molecularly dispersed paliperidone.

In addition, the saturation solubility of the drug in the microenvironment (Cs) might be increased in the liquisolid systems due to the presence of Tween 80. So, such an increase in Cs, in a larger drug concentration gradient, increases the dissolution rate of paliperidone according to the Noyes Whitney equation (Dinesh M. Pardhi et al., 2010 & Nokhodchi A. *et al*., 2005).

12. SELECTION AND EVALUATION OF BEST FORMULATION

From the above results of characterization F20 was selected as the best formulation.

1. Solubility of drug in Tween 80 – 14.252 (mg/10ml)

2. In vitro release studies - 99.24% at 60 min

1. Comparison of dissolution studies of best formulation with pure drug and directly compressed tablets

The *in vitro* dissolution studies of best formulation (F20) were compared with pure drug and directly compressed tablets. The cumulative percentage of drug in formulation was found to be 99.24% in 1 hour compared to the pure drug and directly compressed tablets whose cumulative percentage drug release was found to be

16.50% & 35.20% in 1 hour, respectively. Thus the formulation F20 showed higher drug release than the pure drug and directly compressed tablets. The results were shown in **Table 19** and **Figure 13**.

2. Infrared spectroscopic studies

Infrared spectrum was performed for the liquisolid formulation, the major peaks of the drug still shown in the spectrum at 3343.71 cm^{-1}, 2902 cm^{-1}, 1633.76 cm^{-1}, 1537.32 cm^{-1}, 1429.30 cm^{-1}, 1337.68 cm^{-1}, 1281.74 cm^{-1}, 1112.96 cm^{-1}, 1031.95 cm^{-1}, 898.86 cm^{-1} indicated that there was no interaction between the drug and polymers in the preparation of liquisolid compacts. The result was shown in **Figure 7f**.

3. Differential scanning colorimetric studies

The DSC thermogram of pure drug, excipients and final formulation were shown in **Figure 8a to 8d.** Pure paliperidone showed a sharp endothermic peak at 187˚C corresponding to its melting temperature. Such sharp endothermic peak signifies that paliperidone used was in pure crystalline state. Microcrystalline cellulose showed sharp endothermic peak at 100.50 ˚C. The thermal behavior of aerosil 200 did not show any sharp endothermic peak and hence, the aerosil 200 was in an almost amorphous state. The sharp endothermic peak of pure drug was not observed in final formulation, which indicates that the paliperidone was molecularly dispersed and in an amorphous form (Sanjeev Gubbi *et al*., 2009 and Abdul Hasan Sathali A. and Deepa C. *et al*., 2013).

4. Scanning electron microscopy analysis

The surface morphology of liquisolid tablets was scanned using scanning electron microscopy. The result was shown in **Figure 14**.

The photomicrographs of the liquisolid system signify the complete disappearance of paliperidone crystals. It indicates that the drug was completely solubilized in liquisolid system and also indicates that even though the drug is in solid dosage form, it is held within the powder substrate in solution, almost molecularly dispersed state, which contributes to enhanced dissolution rate of drug (Karmarkar A.B *et al* ., 2009).

5. Stability studies

The stability studies were investigated whether the physical chemical parameters and dissolution of liquisolid tablets is affected by storage under a 40° C ± 2°C and 75%± 5% RH. The best formulation of three batches is stored at 40° C ± 2°C and 75%± 5% RH for two months. The results showed no significant changes in physical appearance, hardness, thickness, drug content and dissolution test of aged tablets compared to the fresh liquisolid tablets. This indicates that the liquisolid tablets were stable under these storage conditions. The results were shown in **Table 20A & 20B & Figure 15.**

TABLES & FIGURES

TABLE 8: CALIBRATION OF PALIPERIDONE IN DISTILLED WATER

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE ± SD*
1.	1	0.030 ± 0.001
2.	2	0.060 ± 0.002
3.	3	0.085 ± 0.001
4.	4	0.113 ± 0.002
5.	5	0.140 ± 0.002
6.	6	0.171 ± 0.002
7.	7	0.198 ± 0.001
8.	8	0.228 ± 0.002
9.	9	0.258 ± 0.001
10.	10	0.286 ± 0.002

n=3* **γ = 0.9998**

TABLE 9: DETERMINATION OF SOLUBILITY OF PALIPERIDONE USING DIFFERENT NON-VOLATILE LIQUID VEHICLES

S.NO	NON-VOLATILE LIQUID VEHICLES	SOLUBILITY (mg/10 ml) ± SD*
1.	PROPYLENE GLYCOL	9.503 ± 0.10
2.	PEG 400	8.331 ± 0.19
3.	TWEEN 80	14.252 ± 0.17
4.	CAPRYOL 90	8.770 ± 0.10
5.	DISTILLED WATER	1.208 ± 0.09

n=6*

PEG 400 = Polyethylene Glycol 400, TWEEN 80= Polysorbate 80, CAPRYOL 90= Propylene Glycol Monocaprylate.

TABLE 10A: COMPOSITION OF PALIPERIDONE LIQUISOLID TABLET

Formulation code	Non-volatile liquid vehicle	Drug : liquid vehicle ratio	R	Active ingredient (mg)	Liquid vehicle (mg)	Lf	Avicel PH102 Q (mg)	Aerosil 200 q (mg)	Disintegrant [SSG (5%)] (mg)	Magnesium stearate [0.75%] (mg)	Total weight of tablet (mg)
F1	Tween 80	1:1	20	6	6	0.200	59.85	2.99	3.74	0.58	79.17
F2	Tween 80		30	6	6	0.134	89.11	2.97	5.20	0.81	110.10
F3	Tween 80	1:2	20	6	12	0.200	89.78	4.49	5.61	0.88	118.76
F4	Tween 80		30	6	12	0.134	133.66	4.45	7.80	1.22	165.15
F5	Tween 80	1:3	20	6	18	0.200	119.70	5.98	7.48	1.17	158.34
F6	Tween 80		30	6	18	0.134	178.21	5.94	10.40	1.63	220.20
F7	Tween 80	1:4	20	6	24	0.200	149.62	7.48	9.35	1.47	197.93
F8	Tween 80		30	6	24	0.134	222.77	7.42	13.00	2.04	275.25
F9	Tween 80	1:5	20	6	30	0.200	179.55	8.97	11.22	1.76	237.52
F10	Tween 80		30	6	30	0.134	267.33	8.91	15.61	2.45	330.30

Tween 80= Polysorbate 80, R = Carrier and coating material ratio, L_f =Liquid load factor, $Q = W/L_f$ (Q= Carrier material and W=Total weight of drug and liquid vehicle), q=Q/R (q = Coating material), SSG= Sodium Starch Glycolate.

TABLE 10B: COMPOSITION OF PALIPERIDONE LIQUISOLID TABLET

Formulation code	Non-volatile liquid vehicle	Drug : liquid vehicle ratio	R	Active ingredient (mg)	Liquid vehicle (mg)	Lf	Avicel PH102 Q (mg)	Aerosil 200 q (mg)	Disintegrant [SSG (5%)] (mg)	Magnesium stearate [0.75%] (mg)	Total weight of tablet (mg)
F11	Tween 80	1:6	20	6	36	0.200	209.48	10.47	13.09	2.06	277.11
F12	Tween 80		30	6	36	0.134	311.88	10.39	18.21	2.86	385.35
F13	Tween 80	1:7	20	6	42	0.200	239.40	11.97	14.96	2.35	316.69
F14	Tween 80		30	6	42	0.134	356.44	11.88	20.81	3.27	440.41
F15	Tween 80	1:8	20	6	48	0.200	269.33	13.46	16.83	2.65	356.28
F16	Tween 80		30	6	48	0.134	400.99	13.36	23.41	3.68	495.46
F17	Tween 80	1:9	20	6	54	0.200	299.25	14.96	18.71	2.94	395.87
F18	Tween 80		30	6	54	0.134	445.54	14.85	26.01	4.09	550.51
F19	Tween 80	1:10	20	6	60	0.200	329.18	16.45	20.58	3.24	435.45
F20	Tween 80		30	6	60	0.134	490.09	16.33	28.62	4.50	605.56

Tween 80= Polysorbate 80, R = Carrier and coating material ratio, L_f =Liquid load factor, $Q = W/L_f$ (Q= Carrier material and W=Total weight of drug and liquid vehicle), q=Q/R (q = Coating material), SSG= Sodium Starch Glycolate.

TABLE 10C: COMPOSITION OF DIRECTLY COMPRESSED TABLETS

S. No	Ingredients	Quantity for one tablet (mg)
1.	Paliperidone	6
2.	Avicel PH102	490.09
3.	Aerosil 200	16.33
4.	Sodium starch glycolate	25.62
5.	Magnesium stearate	4.03

Total Weight = 542.07mg

TABLE 11: PRECOMPRESSIONAL EVALUATION OF POWDER BLEND

Formulation code	Angle of repose θ ± SD*	Bulk density (g/ml) ± SD*	Tapped density (g/ml) ± SD*	Carr's index (%) ± SD*	Hausner's ratio ± SD*
F1	28.96±0.74	0.206±0.01	0.250±0.00	17.57±2.12	1.20±0.03
F2	27.92±0.79	0.324±0.01	0.367±0.02	11.84±0.60	1.13±0.01
F3	29.35±1.48	0.334±0.01	0.403±0.01	16.98±0.44	1.20±0.00
F4	29.39±0.80	0.495±0.03	0.604±0.04	18.05±1.19	1.22±0.00
F5	28.93±0.68	0.515±0.01	0.640±0.02	19.54±0.77	1.23±0.01
F6	28.18±1.02	0.644±0.00	0.782±0.00	17.63±0.06	1.21±0.00
F7	28.43±0.83	0.657±0.00	0.821±0.00	19.99±0.02	1.24±0.00
F8	28.49±0.86	0.698±0.01	0.824±0.02	15.23±0.46	1.17±0.00
F9	29.00±0.59	0.737±0.00	0.910±0.00	18.75±0.05	1.22±0.00
F10	28.19±0.60	0.763±0.05	0.886±0.07	13.88±1.00	1.15±0.01
F11	26.81±1.13	0.798±0.02	0.967±0.03	17.34±0.59	1.20±0.00
F12	27.55±0.29	0.780±0.03	0.888±0.04	12.16±0.55	1.13±0.00
F13	27.42±0.65	0.807±0.06	0.899±0.07	10.21±0.81	1.10±0.01
F14	24.70±0.92	0.759±0.02	0.827±0.04	8.08±2.23	1.08±0.02
F15	27.02±0.52	0.721±0.01	0.847±0.00	14.82±2.00	1.17±0.02
F16	25.30±1.17	0.791±0.03	0.845±0.04	6.41±0.27	1.06±0.00
F17	27.05±0.66	0.771±0.04	0.874±0.05	11.77±0.70	1.13±0.01
F18	25.45±0.65	0.801±0.02	0.878±0.03	8.75±0.26	1.09±0.00
F19	26.81±1.24	0.805±0.02	0.906±0.03	11.12±0.43	1.12±0.01
F20	25.00±0.25	0.825±0.03	0.916±0.00	9.96±1.44	1.11±0.01

n= 3*

TABLE 12: DRUG CONTENT OF PALIPERIDONE POWDER BLEND

S.NO	FORMULATION CODE	DRUG CONTENT (%) ± SD*
1	F1	98.25±0.35
2	F2	97.90±0.35
3	F3	98.13±0.80
4	F4	98.95±0.35
5	F5	99.64±0.69
6	F6	99.18±0.53
7	F7	99.18±0.20
8	F8	99.30±0.60
9	F9	99.06±0.20
10	F10	99.30±0.35
11	F11	99.30±0.70
12	F12	99.06±0.20
13	F13	99.06±0.40
14	F14	98.83±0.88
15	F15	99.41±0.20
16	F16	98.95±0.35
17	F17	99.30±0.35
18	F18	99.06±1.11
19	F19	99.53±0.20
20	F20	99.64±0.69

n= 3*

TABLE 13: POST COMPRESSIONAL EVALUATION OF LIQUISOLID TABLETS

Formulation code	General appearance	Hardness (kg/cm2)	Thickness (mm)	Weight variation(mg)	Friability (%)	Disintegration Time(sec)
F1	White colour	4	2.52	76.1 - 79.4	0.44	8 min 7 sec
F2	White colour	4	3.21	107.80 - 110.30	0.17	7 min 14 sec
F3	White colour	4	3.48	116.8 - 118.5	0.21	6 min 45 sec
F4	White colour	5	2.45	164.7 - 166	0.11	6 min 33 sec
F5	White colour	5	2.58	157.4 - 159	0.4	6 min 42 sec
F6	White colour	5	3.34	218.9 - 220.4	0.19	6 min 5 sec
F7	White colour	5	2.94	196.5 - 197.3	0.68	6 min 24 sec
F8	White colour	5	4.21	274.5 - 275.2	0.46	5 min 35 sec
F9	White colour	5	3.7	236.2 - 237.5	0.68	6 min 1 sec
F10	White colour	5	4.15	328.9 - 330.1	0.77	5 min 35 sec
F11	White colour	5	4.23	276.3 - 277.2	0.48	5 min 26 sec
F12	White colour	5	4.9	384.8 - 285.2	0.12	5 min 25 sec
F13	White colour	5	3.86	315.8 - 316.5	0.4	5 min 23 sec
F14	White colour	5	5.2	439.5 - 440.2	0.21	5 min 13 sec
F15	White colour	5	4.15	355.2 - 356.2	0.25	5 min 17 sec
F16	White colour	5	3.84	494.5 - 495.4	0.16	4 min 33 sec
F17	White colour	5	4.75	394.8 - 395.7	0.17	5 min 11 sec
F18	White colour	5	4.47	549.7 - 550.5	0.11	4 min 12 sec
F19	White colour	5	4.95	435 - 435.7	0.1	4 min 36 sec
F20	White colour	5	4.92	604.7 - 605.3	0.16	3 min 30 sec

n=3*

TABLE 14: DRUG CONTENT OF PALIPERIDONE LIQUISOLID TABLET

S NO	FORMULATION CODE	DRUG CONTENT (%) ± SD*
1	F1	99.53±0.20
2	F2	99.76±0.52
3	F3	99.76±0.52
4	F4	99.88±0.39
5	F5	99.99±0.34
6	F6	99.88±0.39
7	F7	99.88±0.53
8	F8	99.53±0.20
9	F9	99.41±0.20
10	F10	99.65±0.35
11	F11	99.64±0.60
12	F12	99.30±0.35
13	F13	99.41±0.53
14	F14	99.64±0.69
15	F15	99.41±0.20
16	F16	99.30±0.35
17	F17	99.18±0.20
18	F18	99.53±0.72
19	F19	99.18±0.20
20	F20	99.41±0.40

n=3*

TABLE 15A: PRECOMPRESSIONAL EVALUATION FOR DIRECTLY COMPRESSED TABLETS

S.NO	PARAMETERS	VALUES
1.	Angle of repose ± SD	24.01 ± 0.21
2.	Bulk density ± SD	0.624 ± 0.02
3.	Tapped density ± SD	0.683 ± 0.03
4.	Carr's index ± SD	8.67 ± 0.33
5.	Hausner's ratio ± SD	1.09 ± 0.00
6.	Drug content ± SD	98.95% ± 0.35

TABLE 15B: POST COMPRESSIONAL EVALUATION FOR DIRECTLY COMPRESSED TABLETS

S.NO	PARAMETERS	VALUES
1.	Hardness	5 kg/cm^2
2.	Thickness	4.38 mm
3.	Diameter	12 mm
4.	Weight variation	536.7 – 542.6 mg
5.	Friability	0.23 %
6.	Drug content ± SD	99.41% ± 0.20
7.	Disintegration time	14 min 23 sec

TABLE 16A: *IN VITRO* RELEASE PROFILE OF PALIPERIDONE LIQUISOLID FORMULATION

TIME IN MINUTES	CUMULATIVE PERCENTAGE DRUG RELEASE ± SD*				
	F1	F2	F3	F4	F5
5	8.55±0.63	10.03±0.36	10.87±0.36	12.35±0.63	12.98±0.63
10	13.45±0.96	16.82±0.63	17.24±0.73	19.99±0.63	20.83±0.96
15	22.17±0.96	23.03±0.36	23.88±0.63	24.32±0.36	26.22±0.96
20	29.25±0.73	29.91±1.32	32.45±0.36	34.37±0.96	35.01±0.96
25	33.42±1.32	37.46±0.62	38.75±1.67	41.94±0.63	42.17±0.72
30	45.63±1.58	47.58±0.36	48.03±0.36	49.34±0.97	51.05±0.63
45	54.11±1.59	57.12±0.37	59.26±0.72	63.33±0.64	64.41±1.32
60	64.11±0.62	65.24±0.97	68.03±0.63	70.63±0.64	73.20±0.63

n=3*

TABLE 16B: *IN VITRO* RELEASE PROFILE OF PALIPERIDONE LIQUISOLID FORMULATION

TIME IN MINUTES	CUMULATIVE PERCENTAGE DRUG RELEASE ± SD*				
	F6	F7	F8	F9	F10
5	15.73±0.36	16.78±0.63	18.05±0.63	19.95±0.63	21.63±0.73
10	22.52±0.63	25.05±0.63	26.10±0.36	29.48±0.63	31.38±0.63
15	27.71±0.63	29.20±0.73	33.42±1.26	32.81±0.62	36.19±0.96
20	36.30±0.36	37.80±0.37	40.99±0.36	41.43±0.96	44.41±0.63
25	45.36±0.36	47.92±0.97	50.29±0.63	51.36±0.36	53.94±0.97
30	52.99±1.26	56.20±0.64	60.06±0.64	61.14±0.36	63.94±0.64
45	67.42±0.36	68.74±0.35	71.99±0.98	72.23±0.37	75.68±1.28
60	74.75±0.72	76.50±0.64	79.13±0.61	80.43±0.63	84.95±0.63

n=3*

TABLE 16C: *IN VITRO* RELEASE PROFILE OF PALIPERIDONE LIQUISOLID FORMULATION

TIME IN MINUTES	CUMULATIVE PERCENTAGE DRUG RELEASE ± SD*				
	F11	F12	F13	F14	F15
5	22.48±0.63	23.74±0.63	23.95±0.96	25.01±0.63	26.91±0.63
10	33.07±0.96	34.33±0.36	36.02±0.96	38.55±0.96	38.76±0.36
15	37.26±0.63	38.53±0.63	39.81±0.63	42.56±0.36	45.94±0.96
20	45.69±0.62	49.50±0.63	51.42±0.63	55.67±0.36	57.37±0.97
25	54.59±0.36	57.37±0.62	61.41±0.97	64.20±0.36	66.34±1.27
30	64.60±0.63	68.23±0.96	70.60±0.98	72.36±1.27	73.03±0.65
45	76.55±0.36	79.16±0.36	80.90±0.64	80.98±0.63	82.93±1.28
60	83.09±0.63	85.71±0.63	88.52±0.35	90.28±0.62	93.08±0.99

n=3*

TABLE 16D: *IN VITRO* RELEASE PROFILE OF PALIPERIDONE LIQUISOLID FORMULATION

TIME IN MINUTES	CUMULATIVE PERCENTAGE DRUG RELEASE ± SD*				
	F16	F17	F18	F19	F20
5	31.97±0.63	30.70±1.26	34.08±0.36	32.39±0.36	38.93±0.63
10	42.77±0.63	42.14±0.63	44.67±0.63	42.56±0.36	46.99±0.96
15	49.97±0.63	48.28±0.36	49.98±0.63	48.49±0.36	54.42±0.63
20	61.01±0.63	60.15±0.96	62.91±0.63	60.57±0.36	64.85±0.63
25	69.15±0.97	67.23±0.37	69.80±0.36	68.29±0.63	72.59±0.97
30	77.54±0.64	75.19±0.37	78.20±1.68	75.42±0.36	79.53±0.64
45	86.83±0.64	84.89±0.64	88.97±1.33	87.01±0.97	91.99±1.28
60	96.79±0.65	95.48±0.64	98.10±0.65	94.24±0.62	99.24±0.35

n=3*

TABLE 17: DISSOLUTION RATE OF DRUG AFTER 10 MIN

S.NO	FORMULATION CODE	DISSOLUTION RATE AFTER 10 MIN (µg/min)
1	F1	80.70
2	F2	100.95
3	F3	103.49
4	F4	119.94
5	F5	125.00
6	F6	135.13
7	F7	150.32
8	F8	156.65
9	F9	176.90
10	F10	188.29
11	F11	198.42
12	F12	206.02
13	F13	216.14
14	F14	231.33
15	F15	232.60
16	F16	256.65
17	F17	252.85
18	F18	268.04
19	F19	255.38
20	F20	281.96

TABLE 18: COMPARISON OF DISSOLUTION RATE OF PURE DRUG, CONVENTIONAL TABLET AND BEST FORMULATION AFTER 10 MIN

DISSOLUTION RATE AFTER 10 MIN (µg/min)	
PURE DRUG	33.87
CONVENTIONAL TABLET	71.84
BEST FORMULATION	281.96

TABLE 19: COMPARISON OF *IN VITRO* RELEASE PROFILE FOR PURE DRUG, CONVENTIONAL TABLET AND LIQUISOLID TABLET

CUMULATIVE PERCENTAGE DRUG RELEASE ± SD*								
TIME IN MINUTES	5	10	15	20	25	30	45	60
PURE DRUG	4.33±0.36	5.64±0.36	6.94±0.36	8.24±0.36	10.40±0.36	11.30±0.00	13.89±0.62	16.50±0.63
CONVENTIONAL TABLET	8.76±0.36	11.97±0.36	15.41±0.36	17.61±0.63	21.50±0.63	23.94±0.97	29.34±0.64	35.20±0.64
LIQUISOLID TABLET	38.93±0.63	46.99±0.96	54.42±0.63	64.85±0.63	72.59±0.97	79.53±0.64	91.99±1.28	99.24±0.35

n=3*

TABLE 20A: STABILITY STUDY OF BEST FORMULATION (F20) AT 40° C ± 2°C AND 75%± 5%

PARAMETERS	INTERVAL OF TESTING		
	AT 0 MONTH	AT 1MONTH	AT 2MONTH
Physical appearance	White colour, biconvex shaped	White colour, biconvex shaped	White colour, biconvex shaped
Hardness ($kg/cm^{2)}$	5	5	5
Thickness (mm)	4.92	4.92	4.92
Drug content (%)±SD	99.41±0.40	99.06±0.72	98.97±0.54

TABLE 20B: DISSOLUTION PROFILE OF BEST FORMULATION (F20) AT 40° C ± 2°C AND 75%± 5%

Time interval (min)	Percentage of drug release		
	AT 0 MONTH	AT 1MONTH	AT 2MONTH
5	38.93±0.63	37.24±0.36	37.03±0.63
10	46.99±0.96	45.30±1.67	45.09±1.82
15	54.42±0.63	52.94±0.72	52.73±0.95
20	64.85±0.63	63.36±1.32	63.35±1.32
25	72.59±0.97	70.88±1.33	70.45±2.04
30	79.53±0.64	78.88±1.33	78.43±1.33
45	91.99±1.28	90.89±1.96	90.68±1.70
60	99.24±0.35	98.14±0.04	97.92±0.36

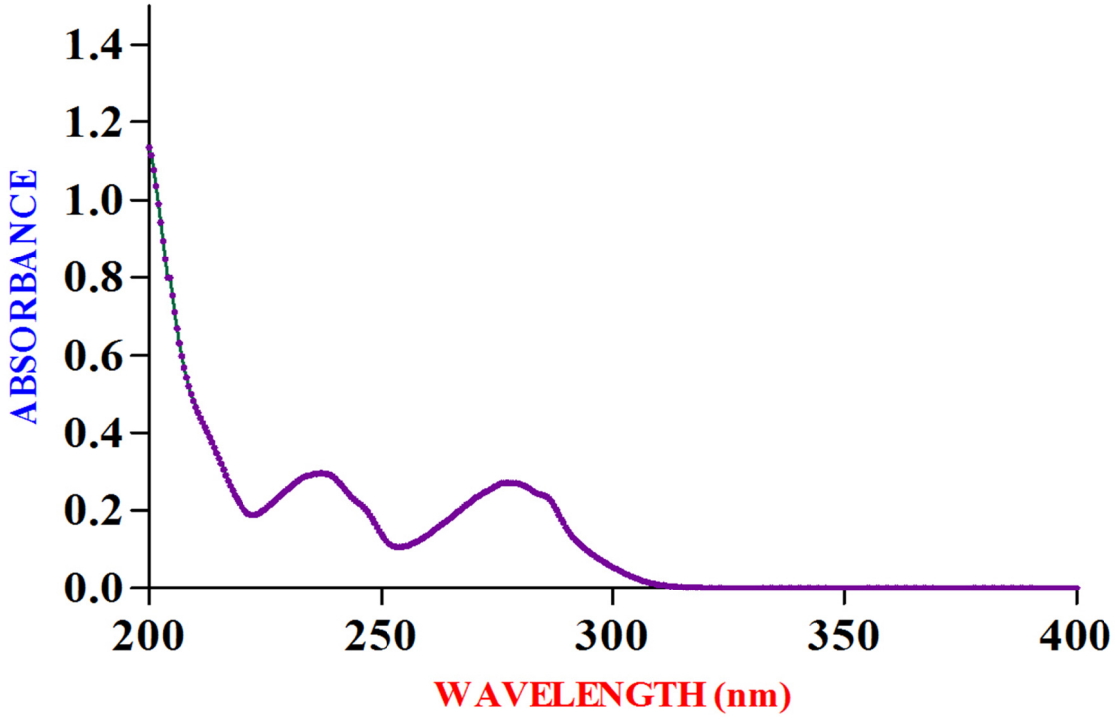

Figure 4: Determination of λmax of paliperidone

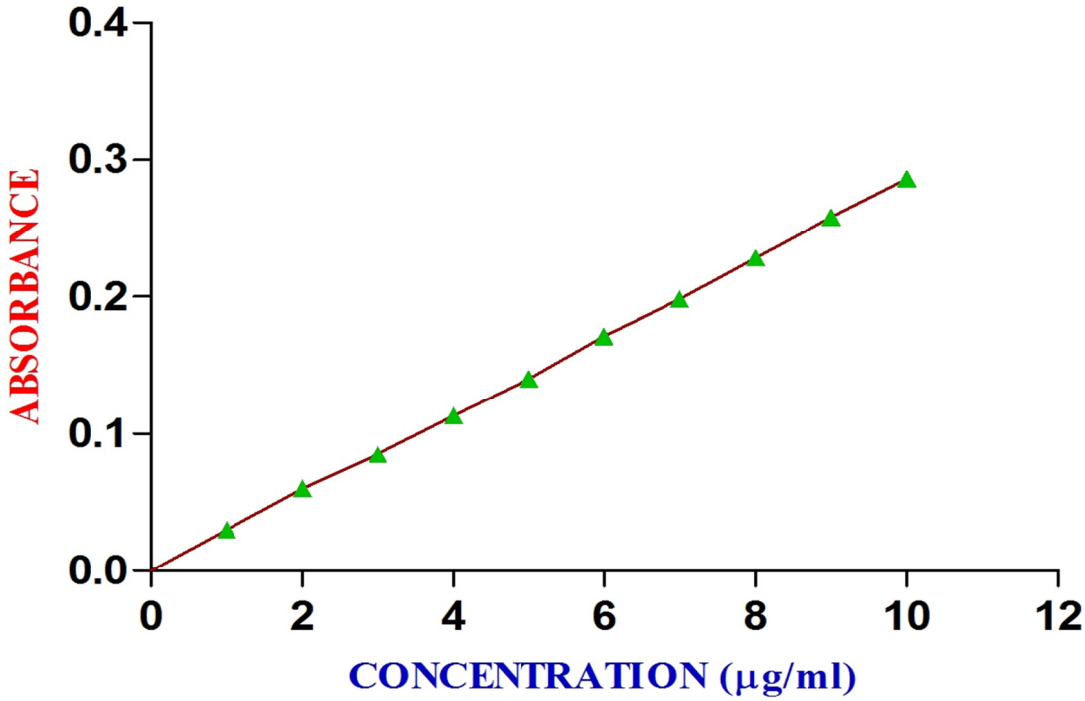

Figure 5: Calibration curve of paliperidone in distilled water

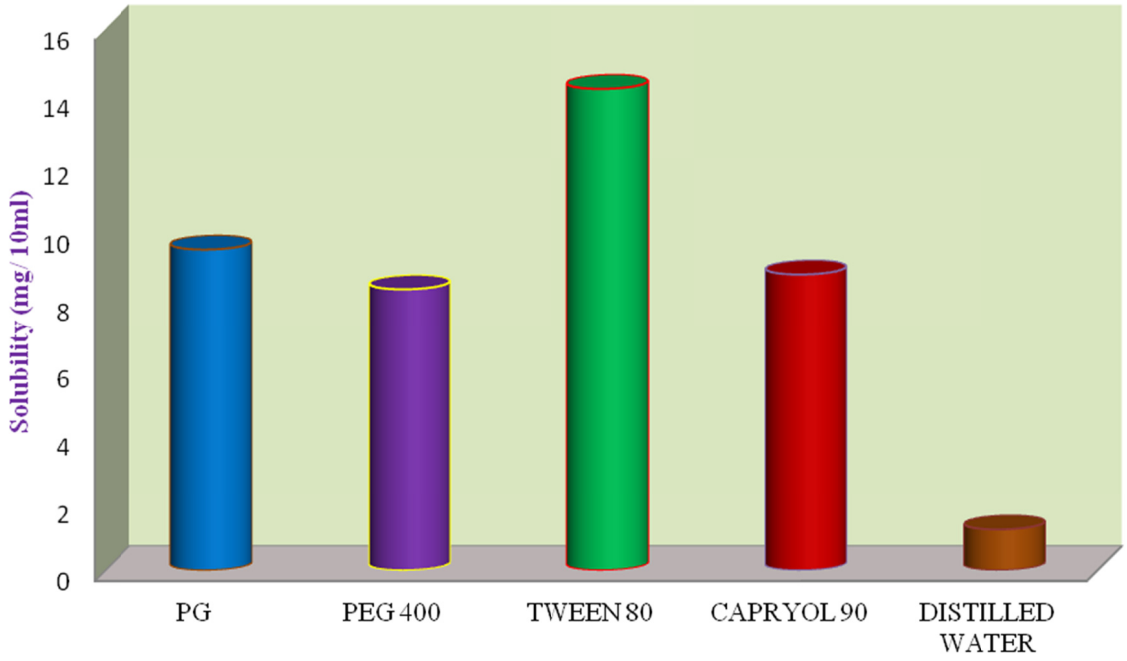

Figure 6: Solubility of paliperidone in various non-volatile liquid vehicles

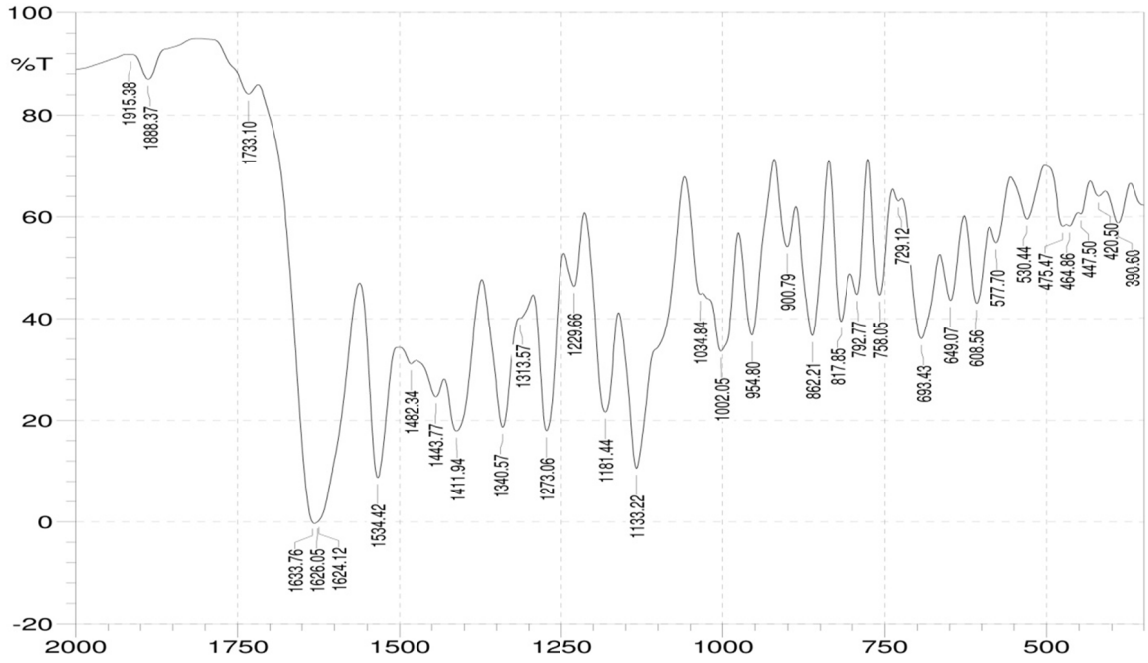

Figure 7a: FT-IR spectrum of paliperidone

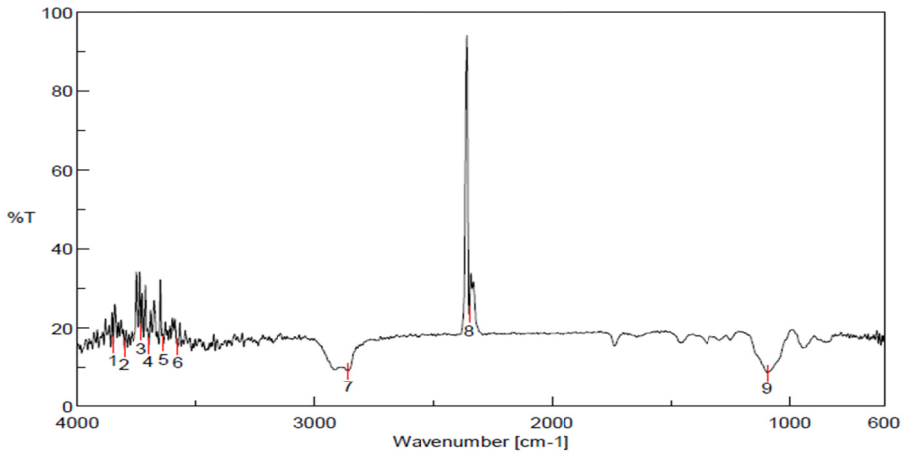

Figure 7b: FT-IR spectrum of Tween 80

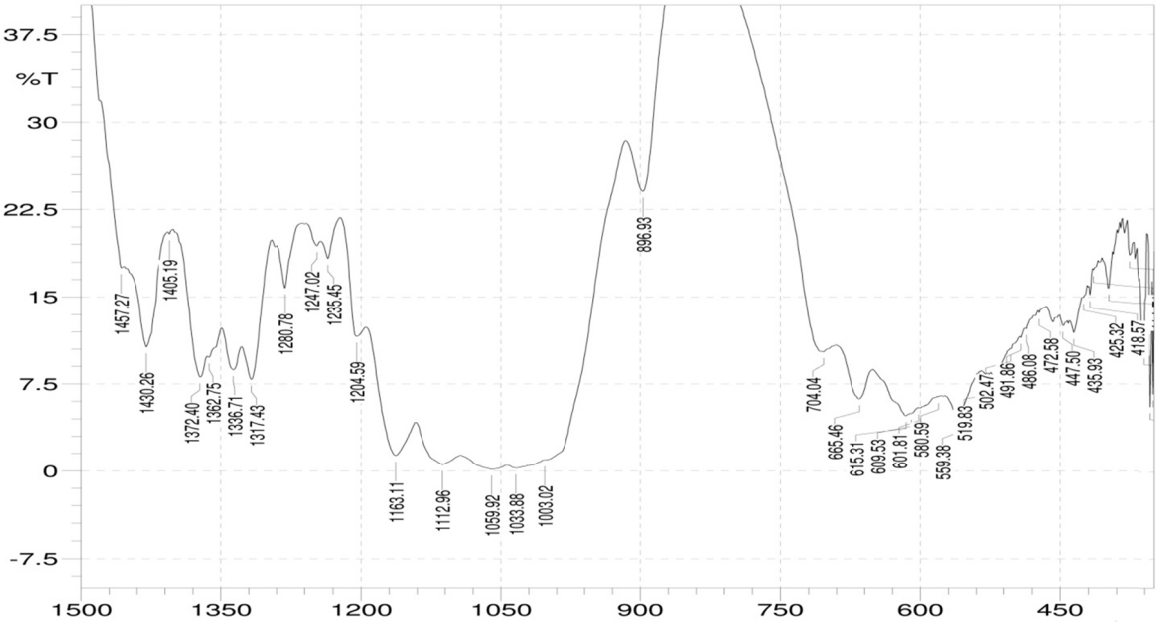

Figure 7c: FT-IR spectrum of microcrystalline cellulose

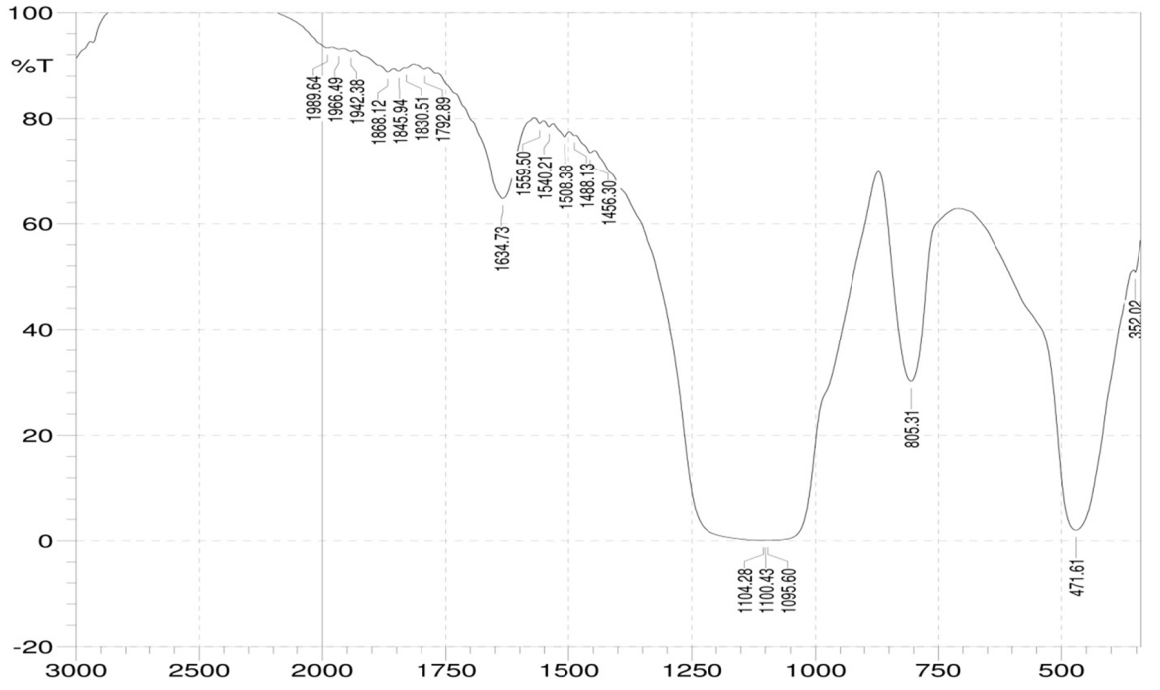

Figure 7d: FT-IR spectrum of aerosil 200

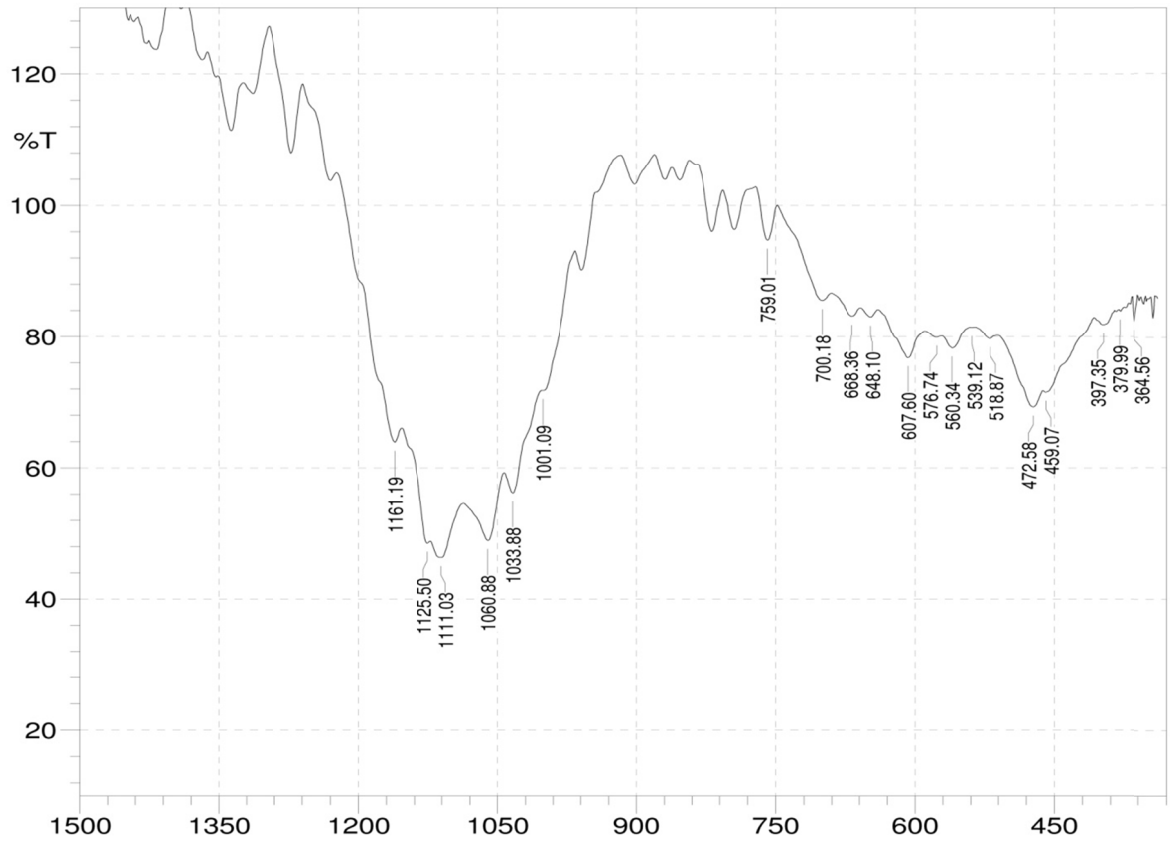

Figure 7e: FT-IR spectrum of Drug + Tween 80 + microcrystalline cellulose + Aerosil 200

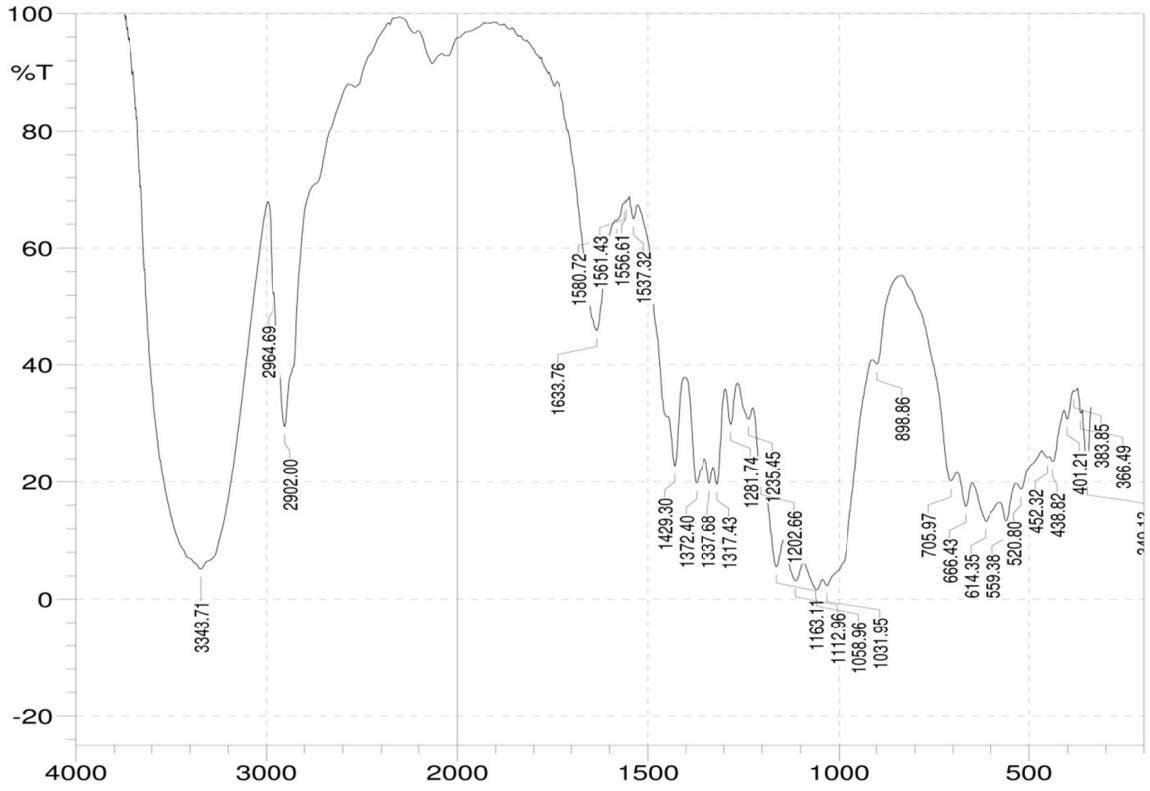

Figure 7f: FT-IR spectrum of liquisolid formulation

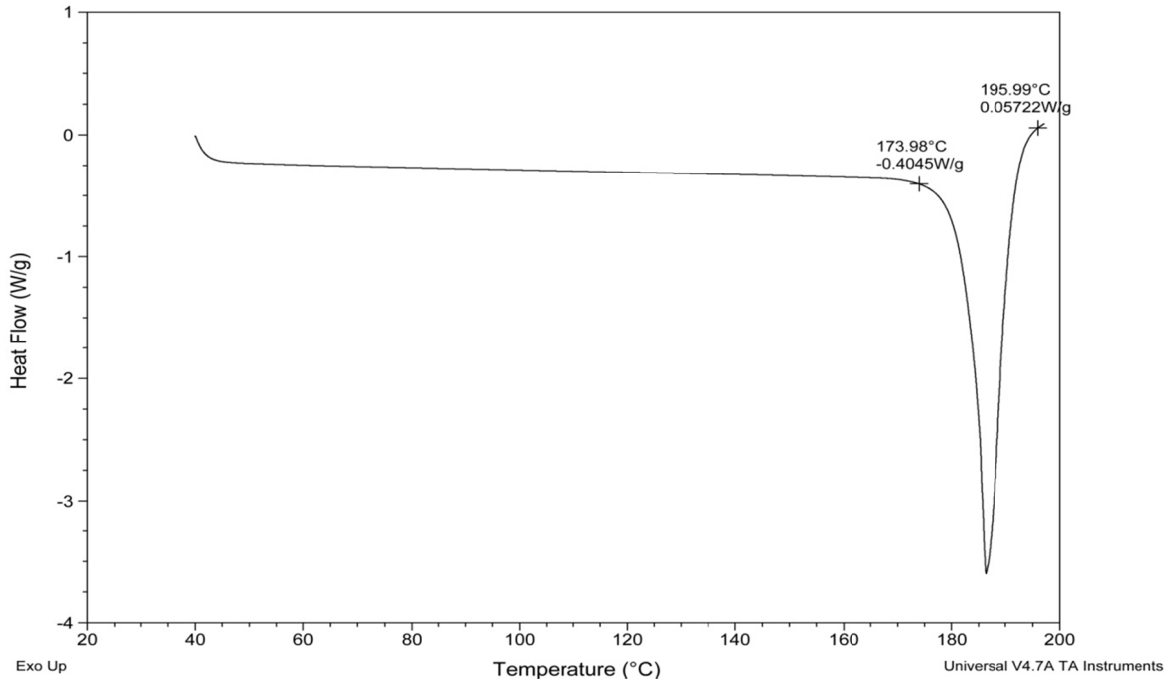

Figure 8a: DSC thermogram of paliperidone

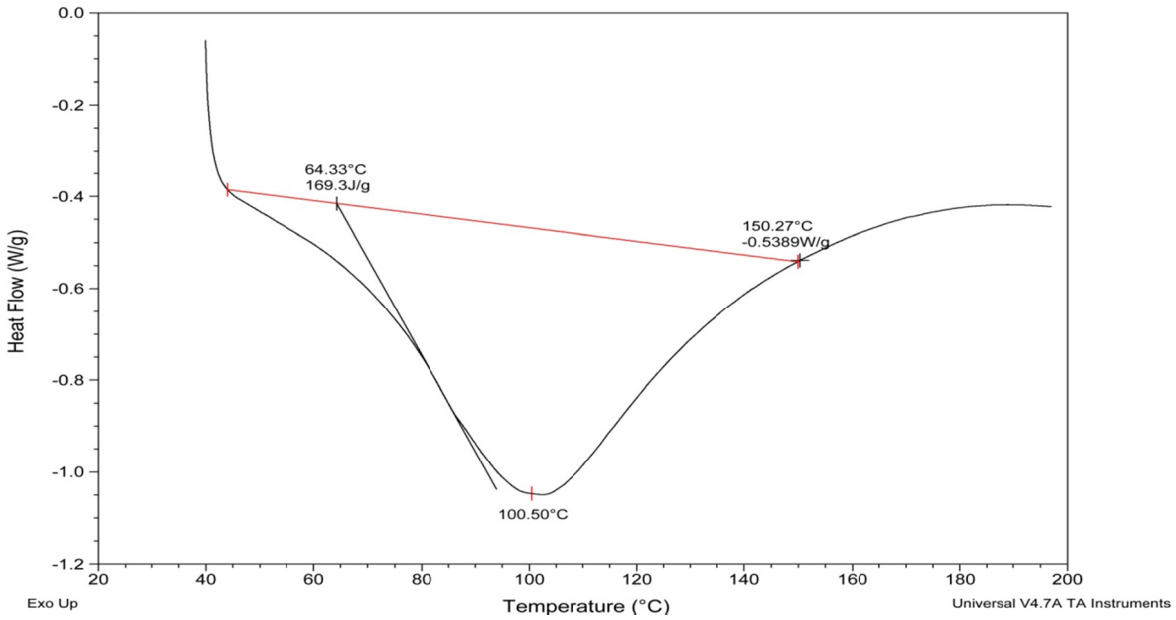

Figure 8b: DSC thermogram of microcrystalline cellulose

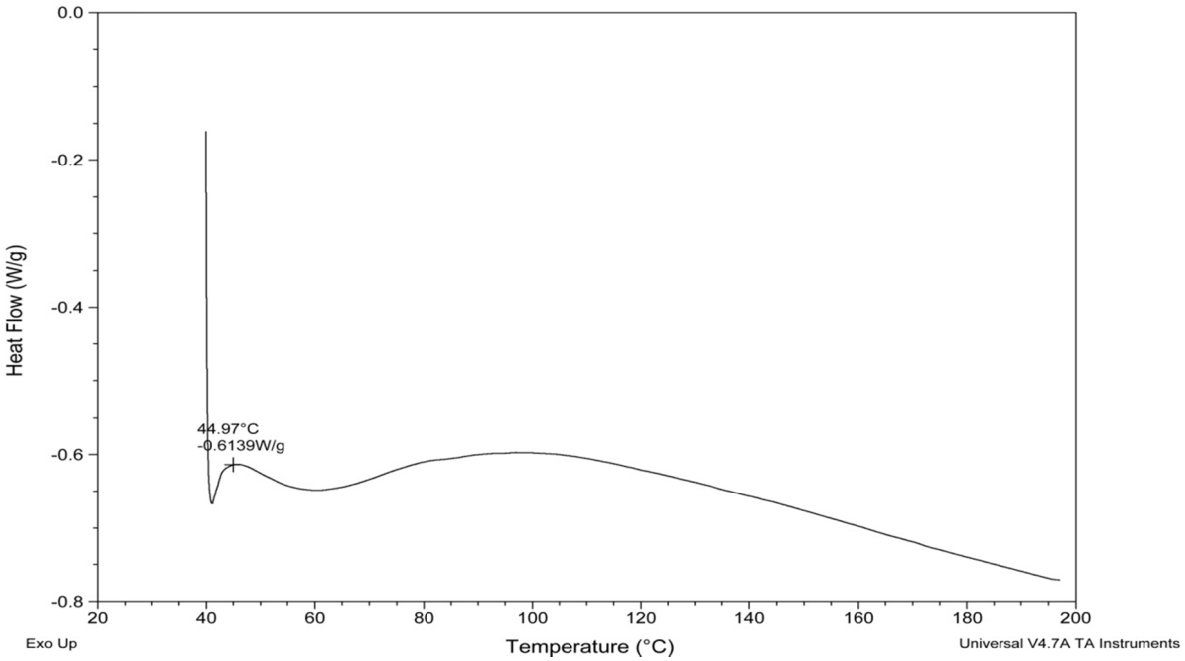

Figure 8c: DSC thermogram of Aerosil 200

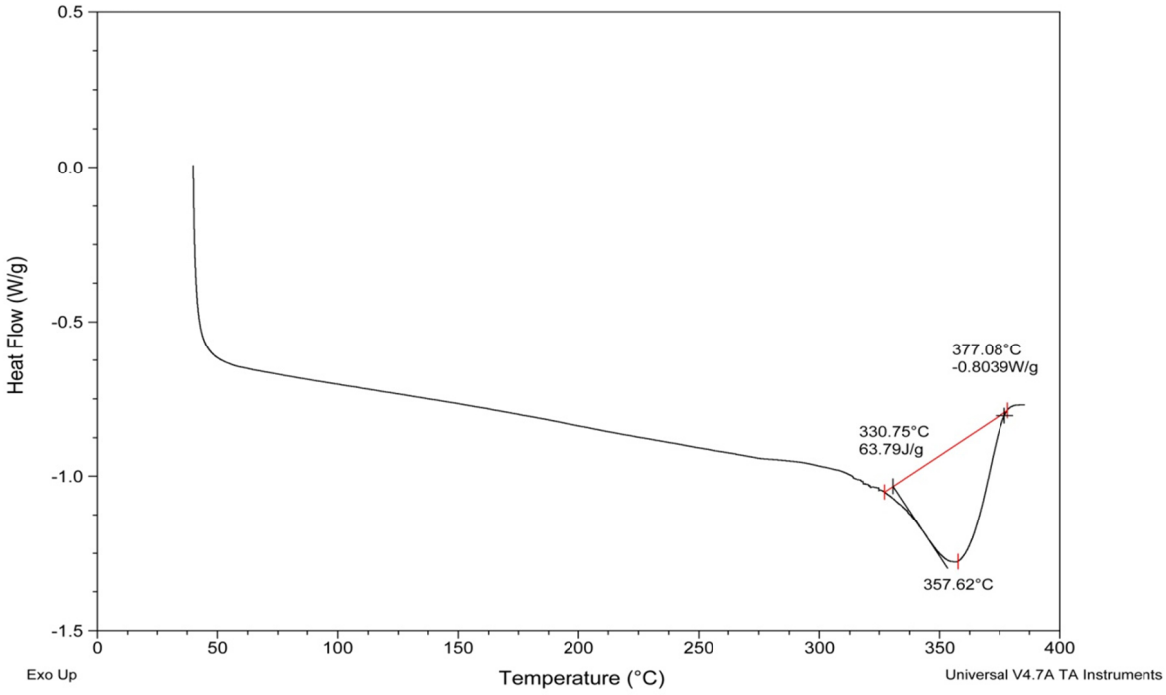

Figure 8d: DSC thermogram of liquisolid formulation

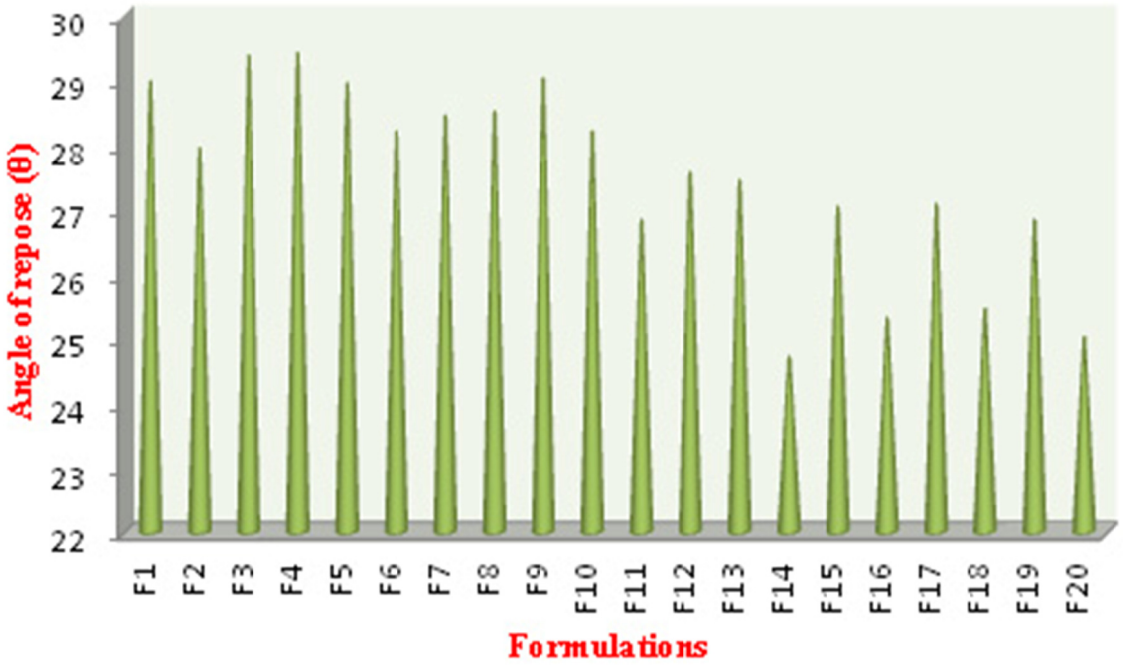

Figure 9a: Angle of repose of all the tablet formulations

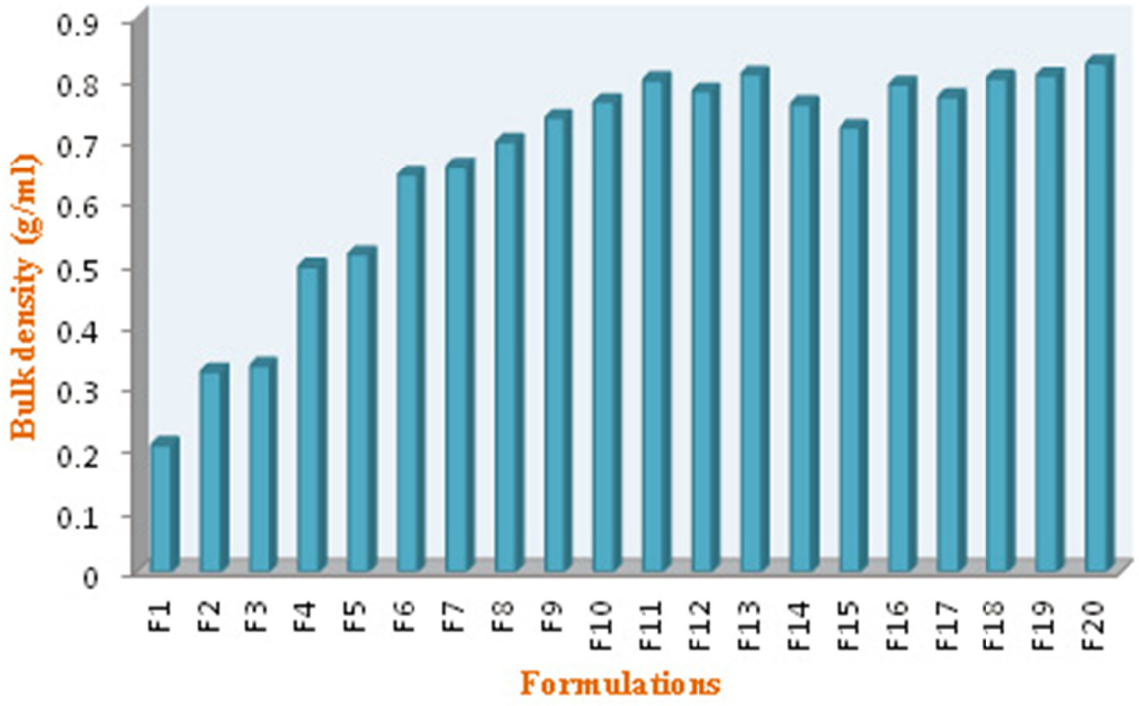

Figure 9b: Bulk density of all the tablet formulations

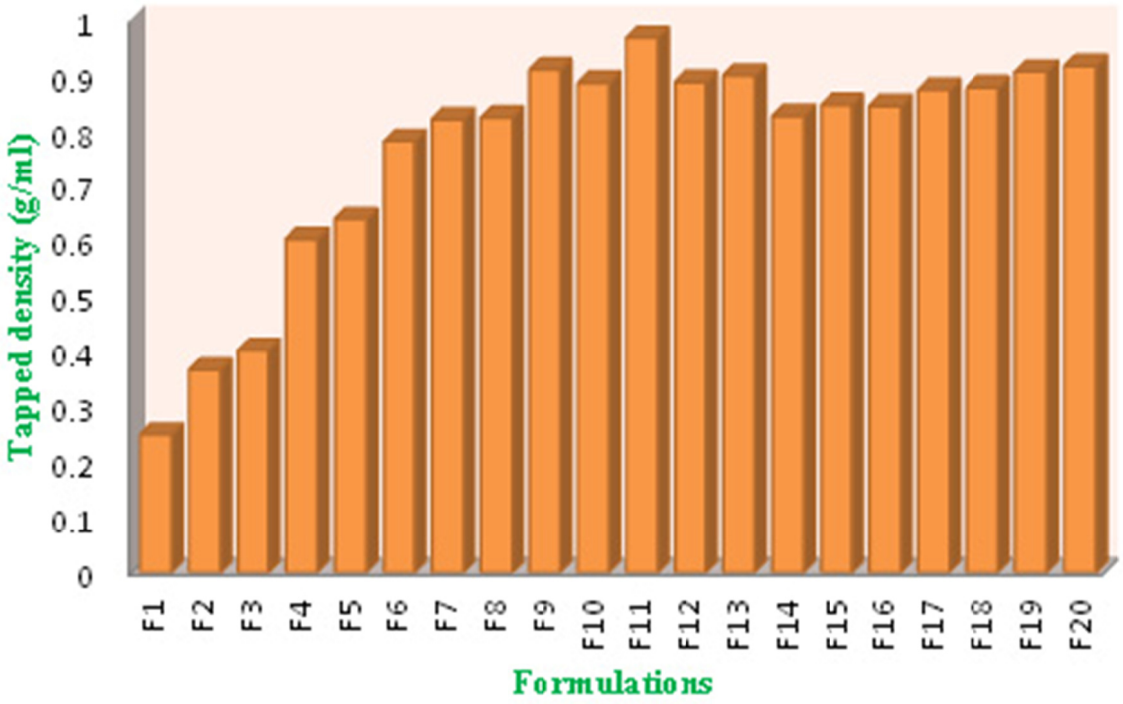

Figure 9c: True density of all the tablet formulations

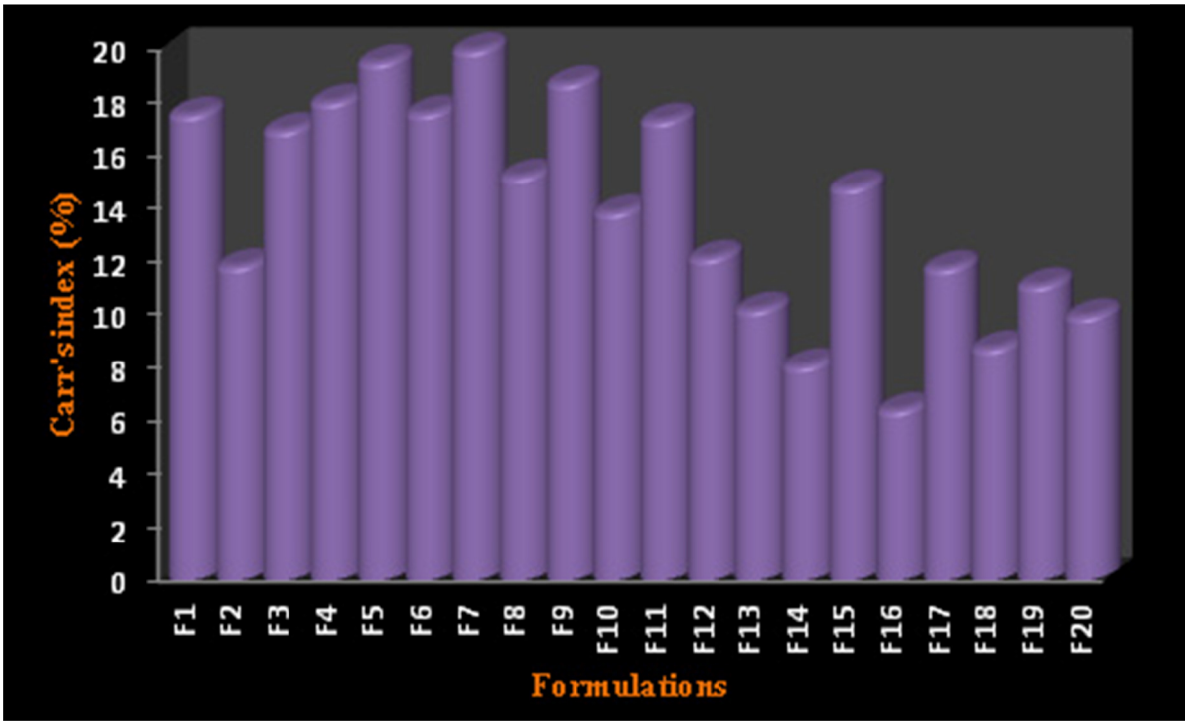

Figure 9d: Carr's index of all the tablet formulations

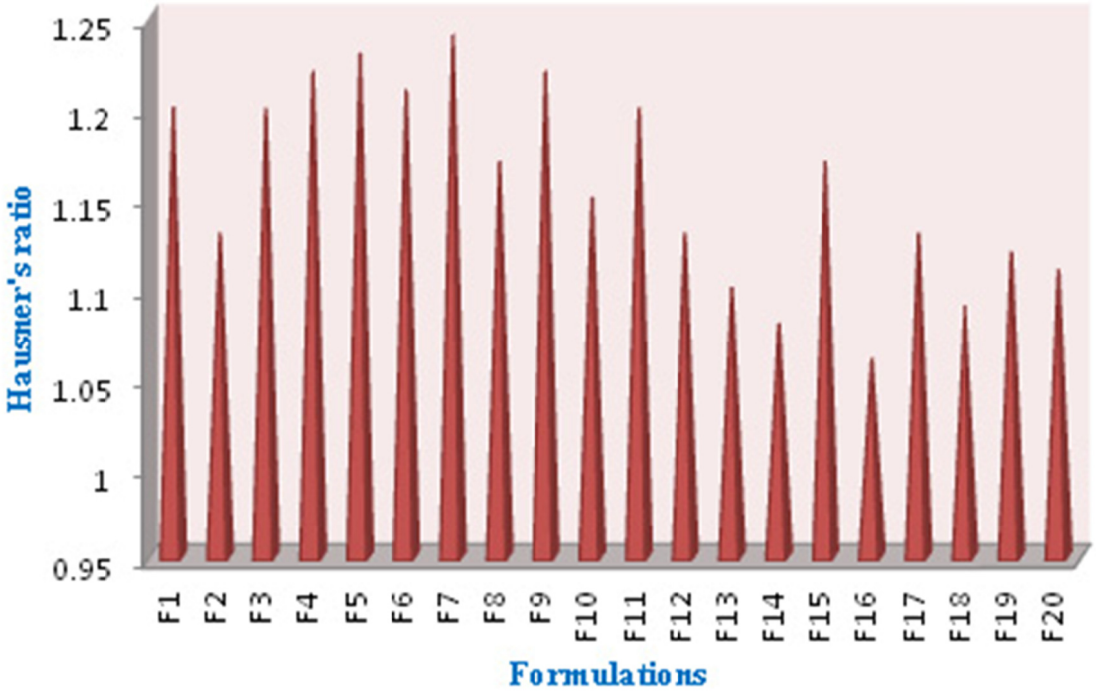

Figure 9e: Hausner's ratio of all the tablet formulations

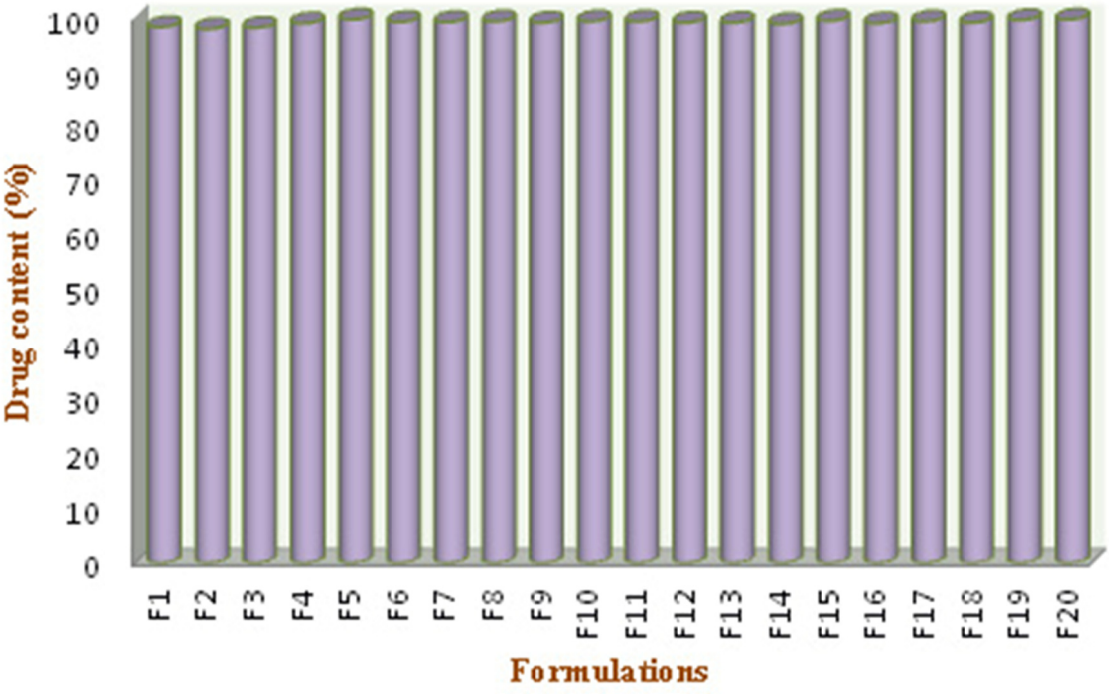

Figure 9f: Drug content of the entire liquisolid powder blend

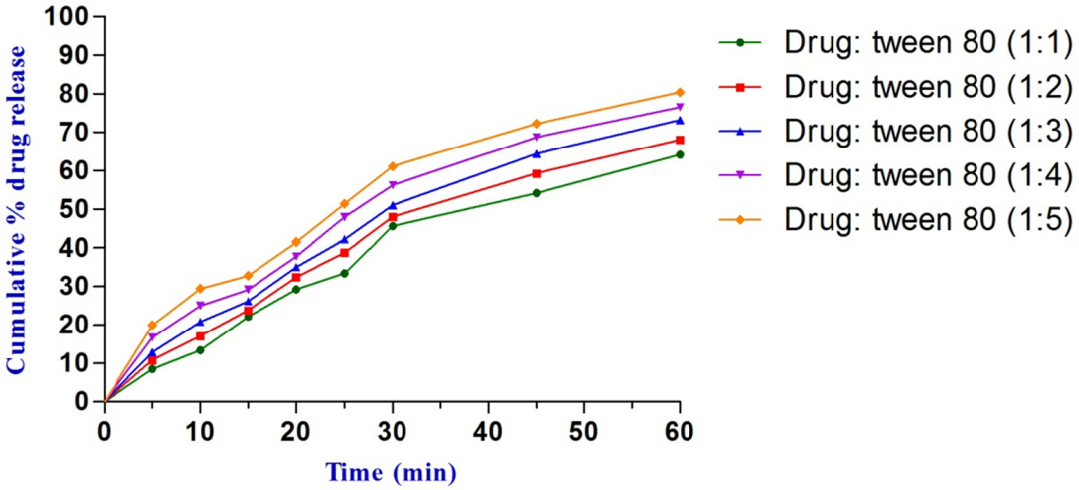

Figure 10a: *In vitro* release profile of liquisolid tablets of paliperidone [MCC: SILICA (20:1)]

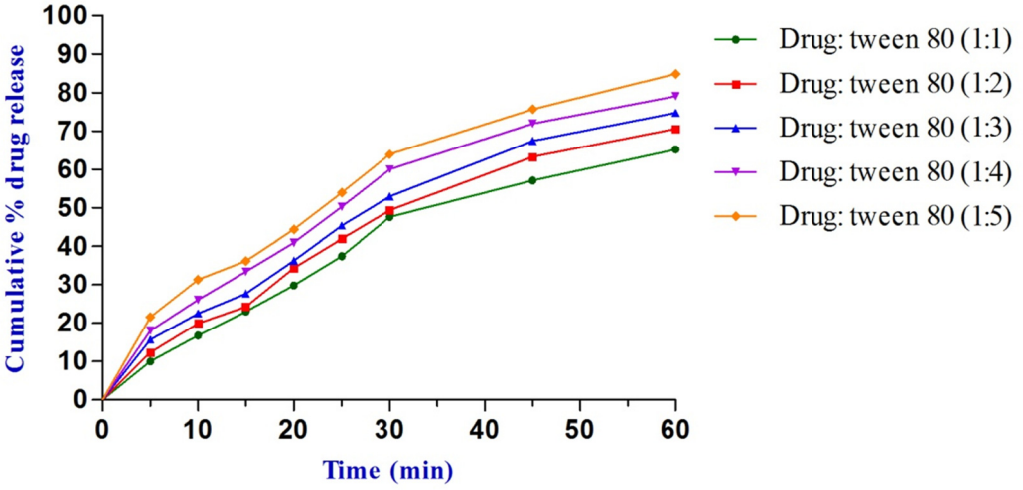

Figure 10b: *In vitro* release profile of liquisolid tablets of paliperidone [MCC: SILICA (30:1)]

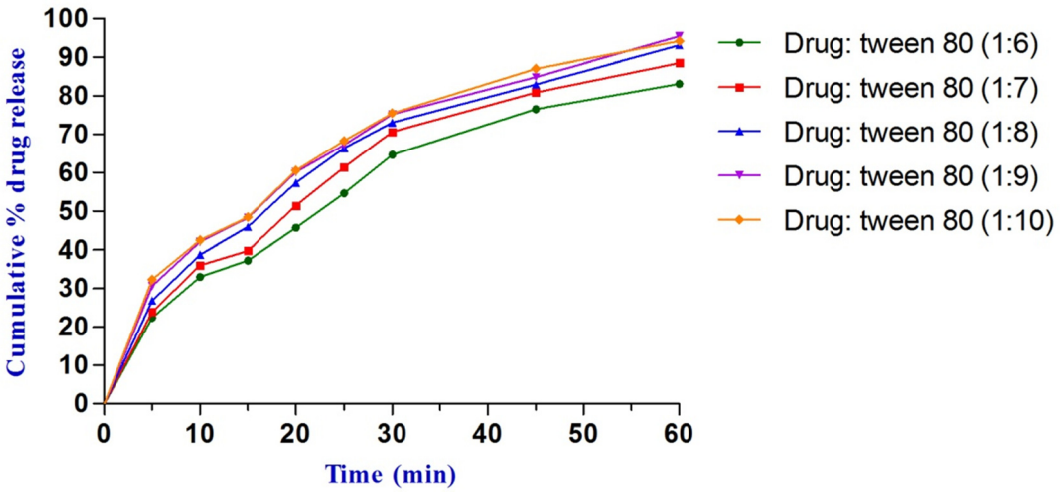

Figure 10c: *In vitro* release profile of liquisolid tablets of paliperidone [MCC: SILICA (20:1)]

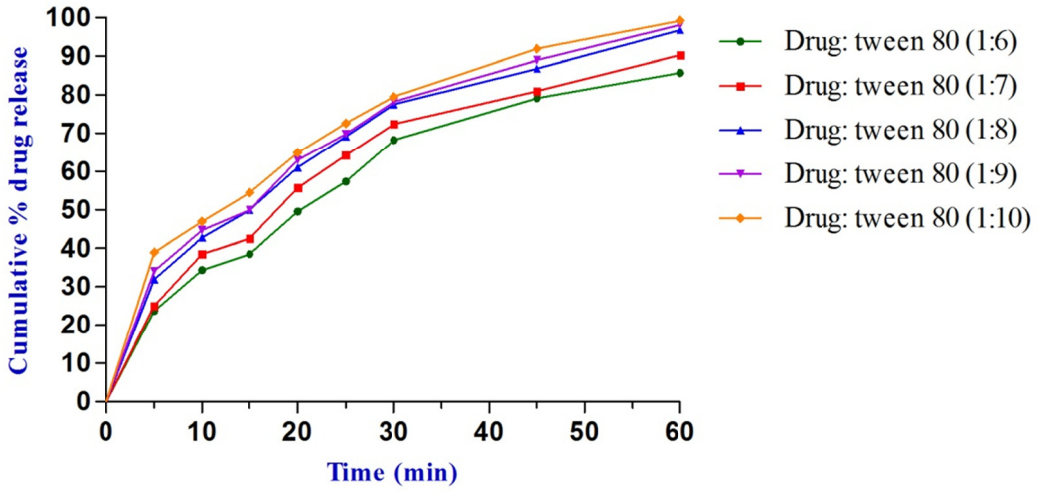

Figure 10d: *In vitro* release profile of liquisolid tablets of paliperidone [MCC: SILICA (30:1)]

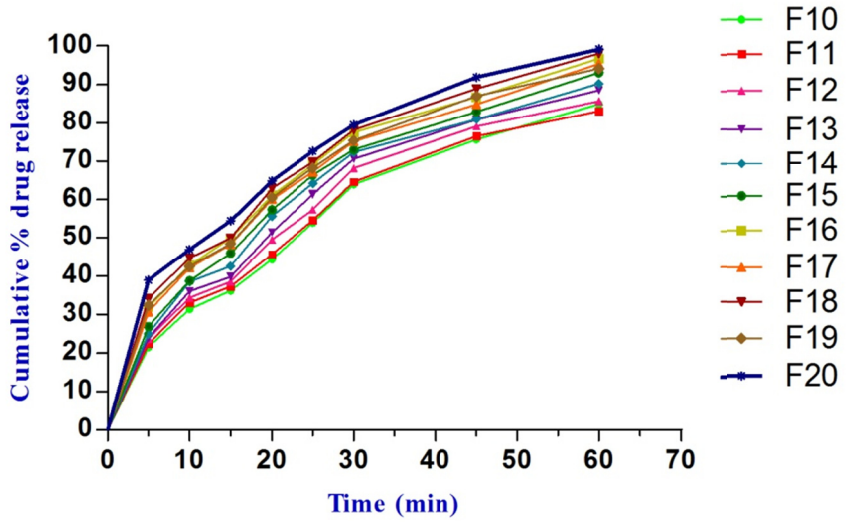

Figure 10e: Comparison of *in vitro* release studies more than 75% within 45 minutes of liquisolid tablets

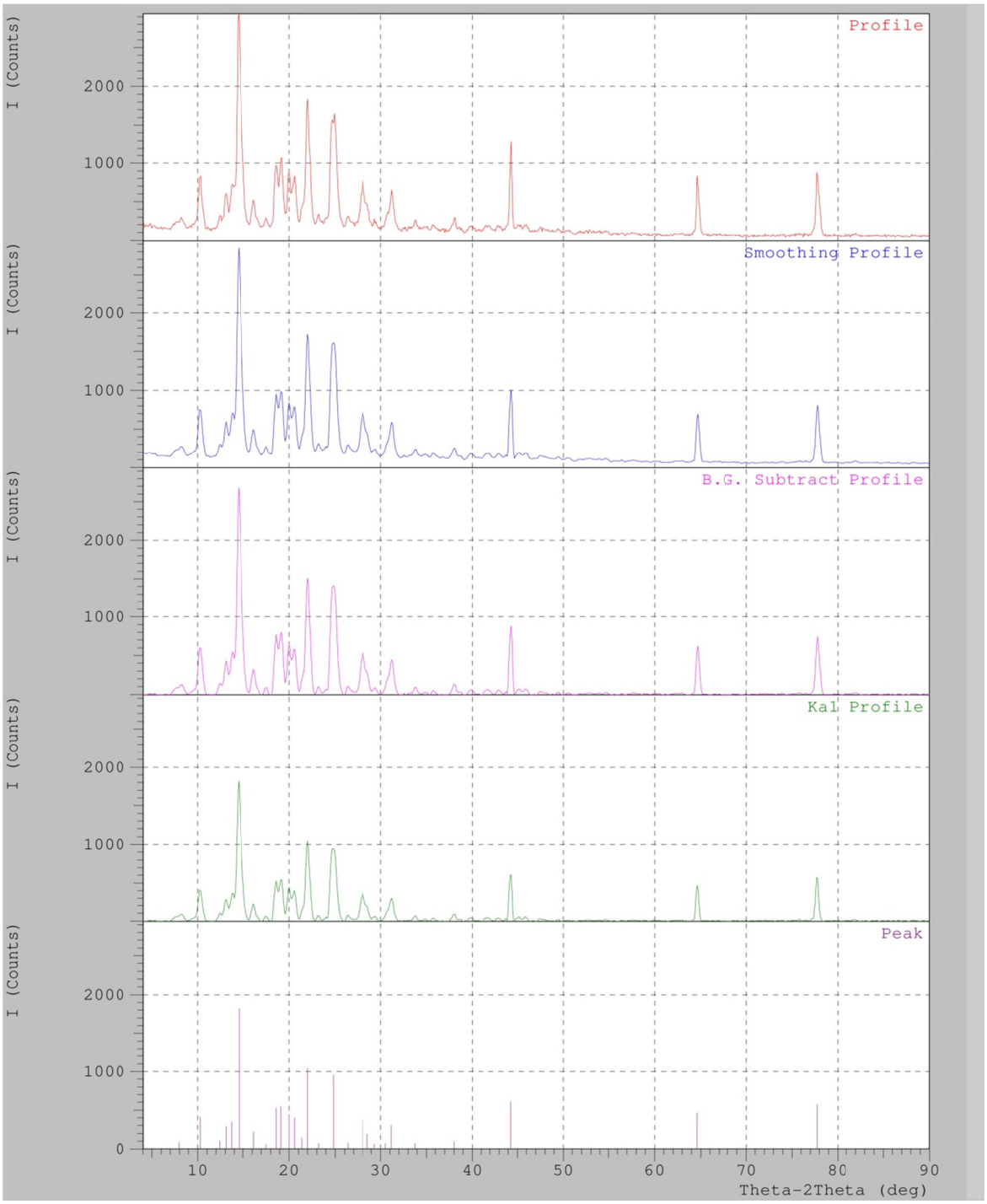

Figure 11a: Powder X-ray diffraction studies for paliperidone

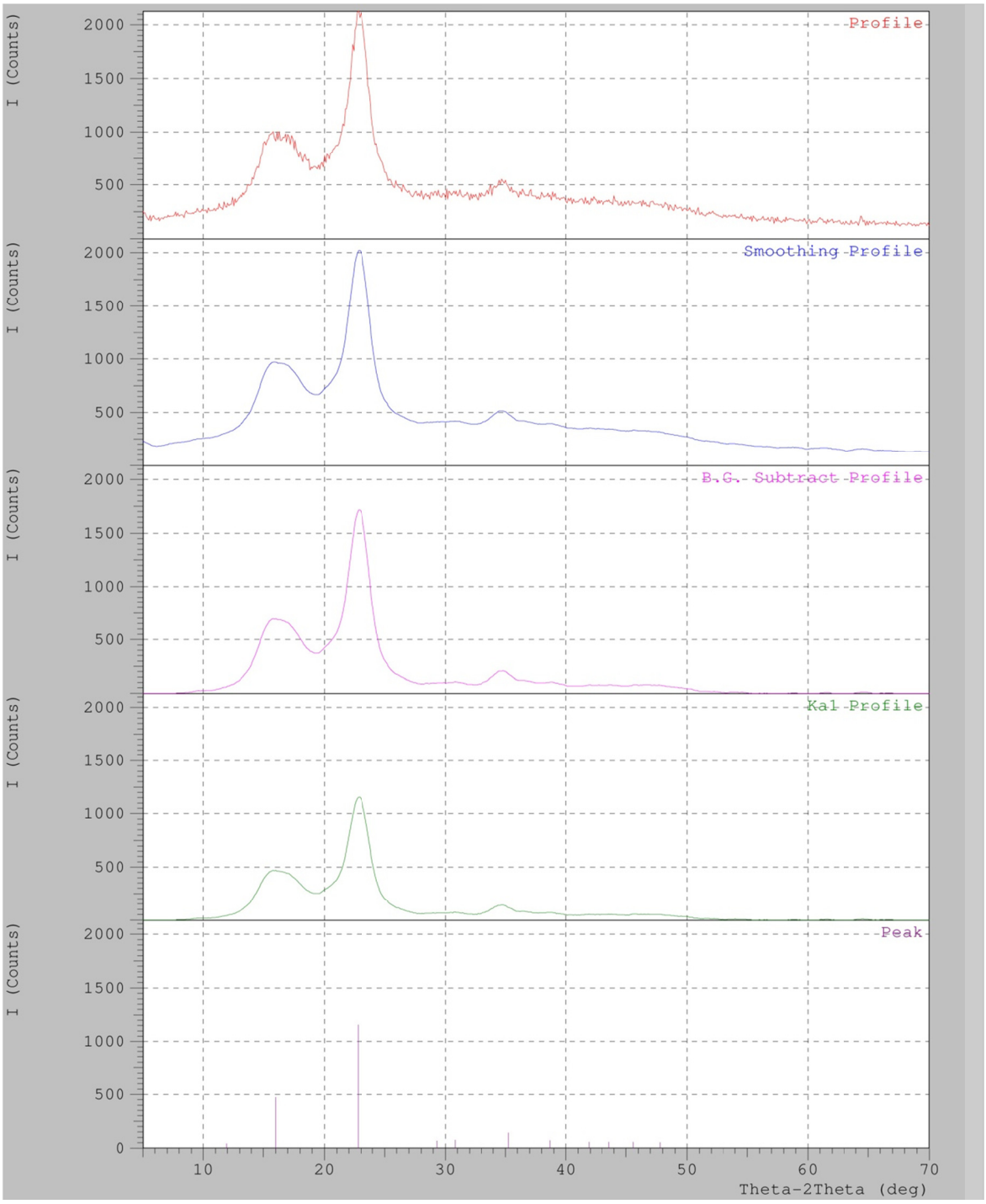

Figure 11b: Powder X-ray diffraction studies for microcrystalline cellulose

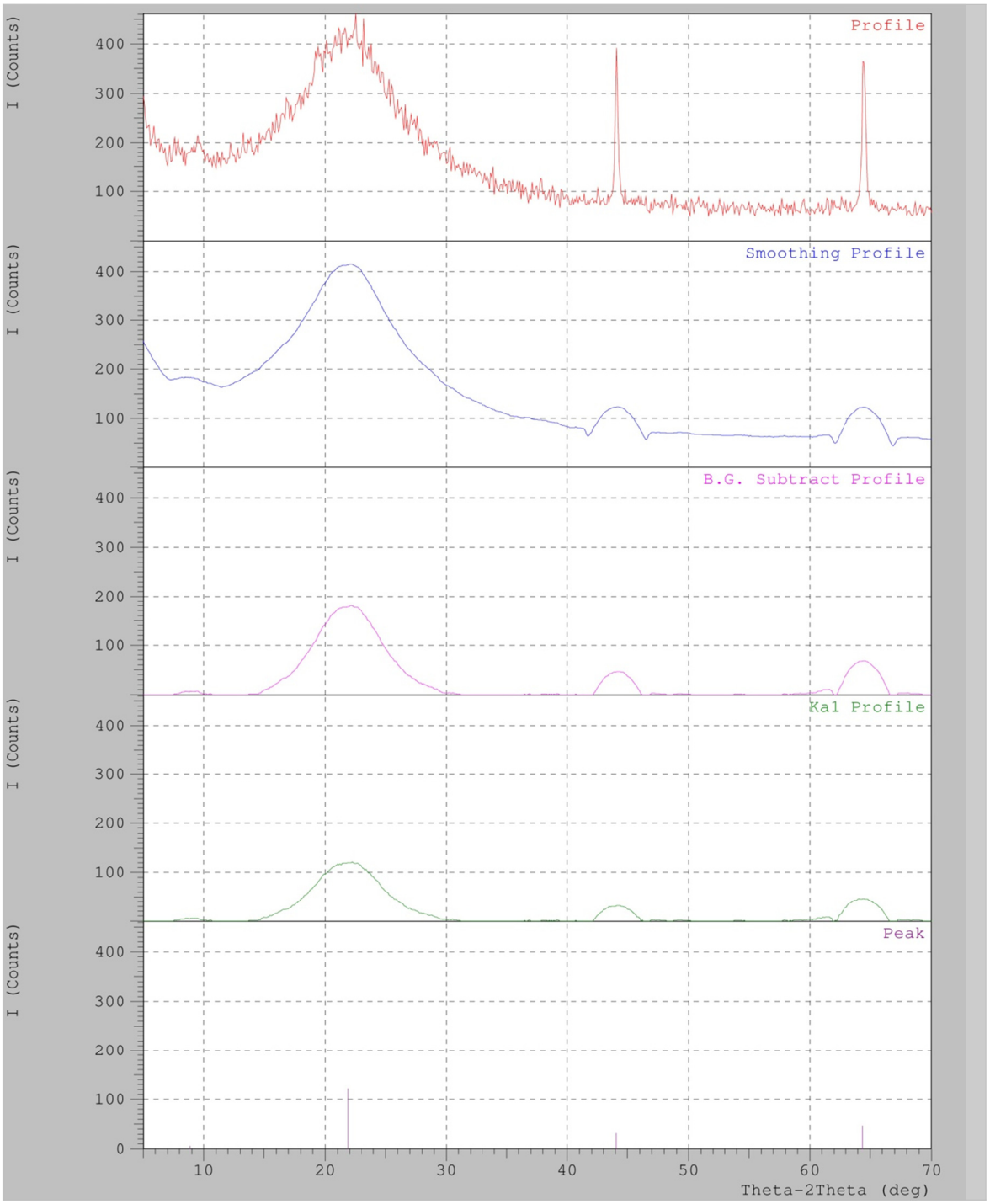

Figure 11c: Powder X-ray diffraction studies for Aerosil 200

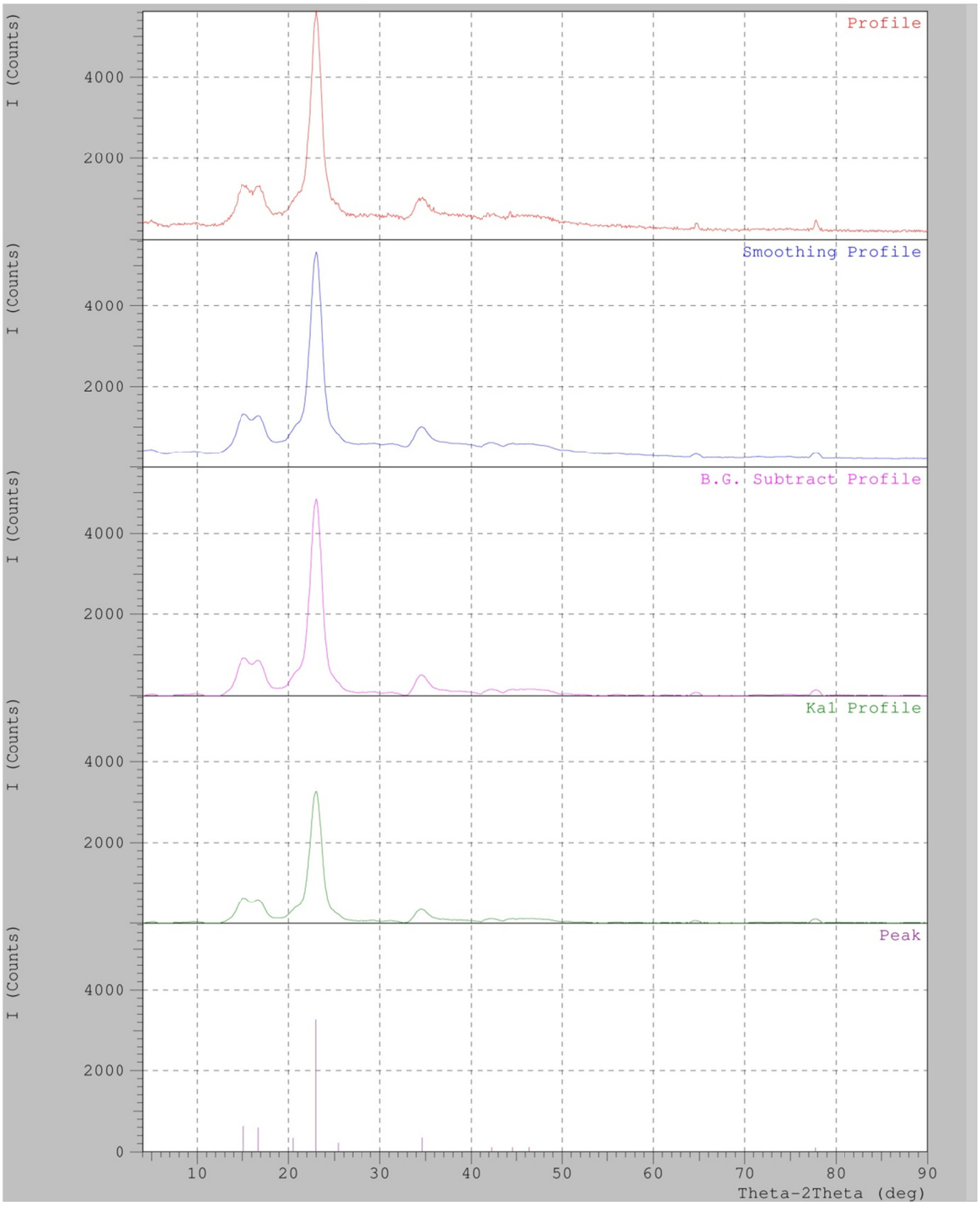

Figure 11d: Powder X-ray diffraction studies for liquisolid formulation

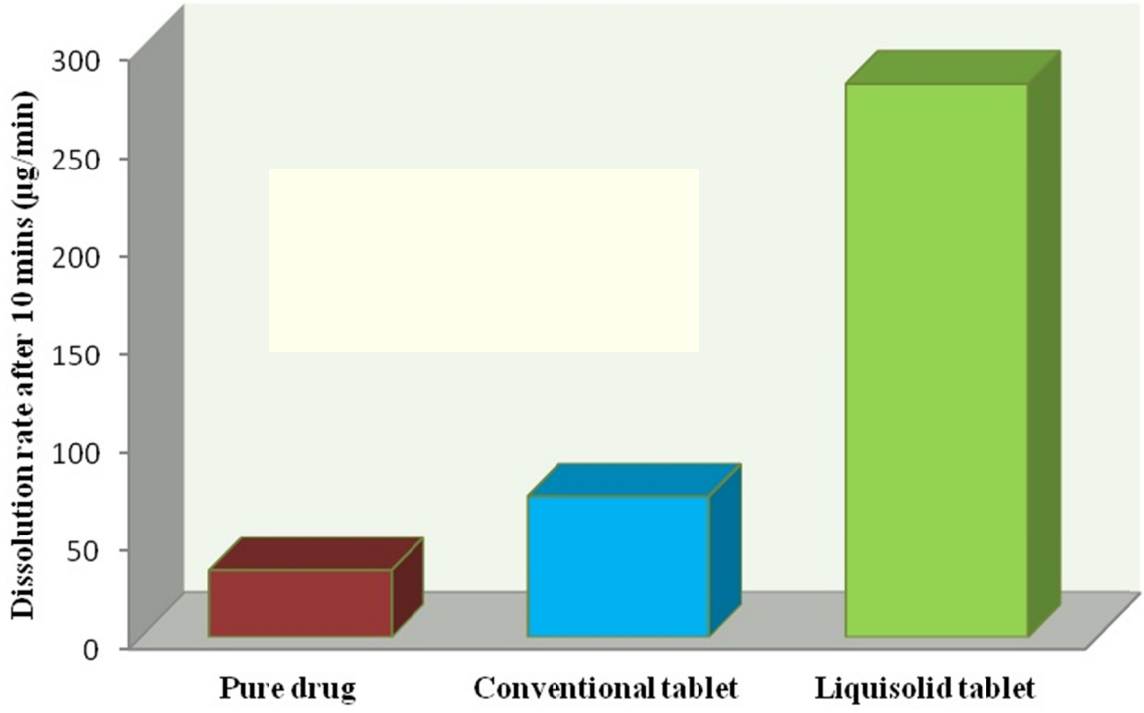

Figure 12: Comparison of dissolution rate after 10 minutes of pure drug, conventional tablet and liquisolid tablet

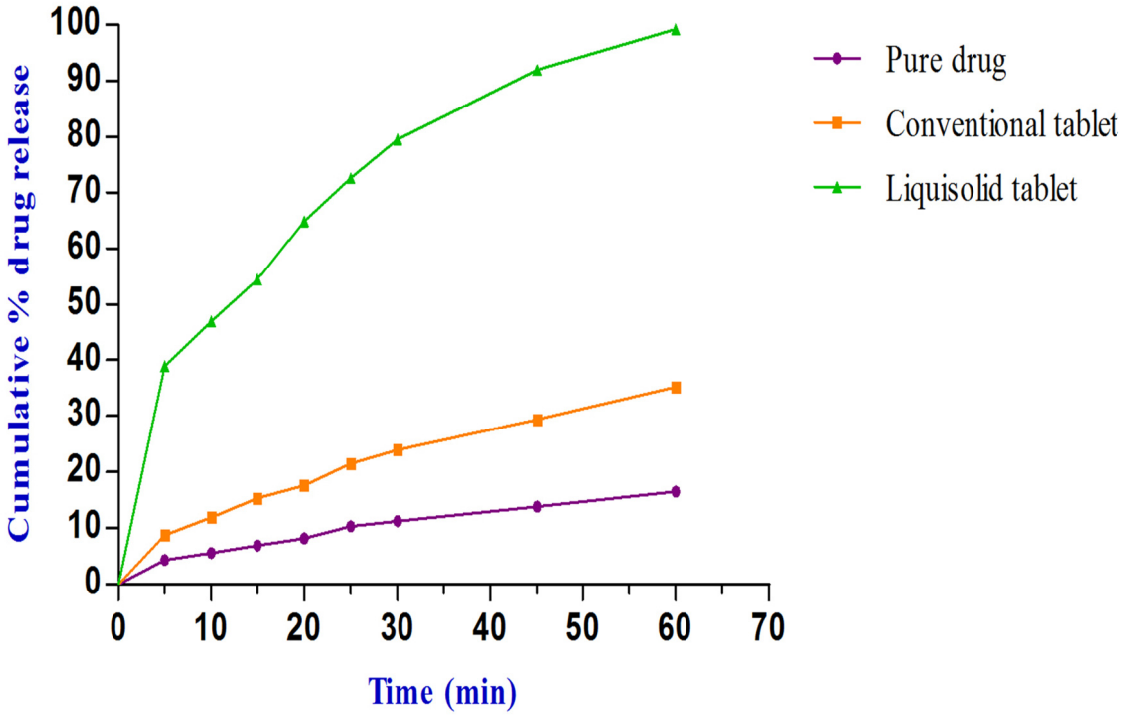

Figure 13: Comparison of *in vitro* release studies liquisolid formulation with pure drug and conventional tablet

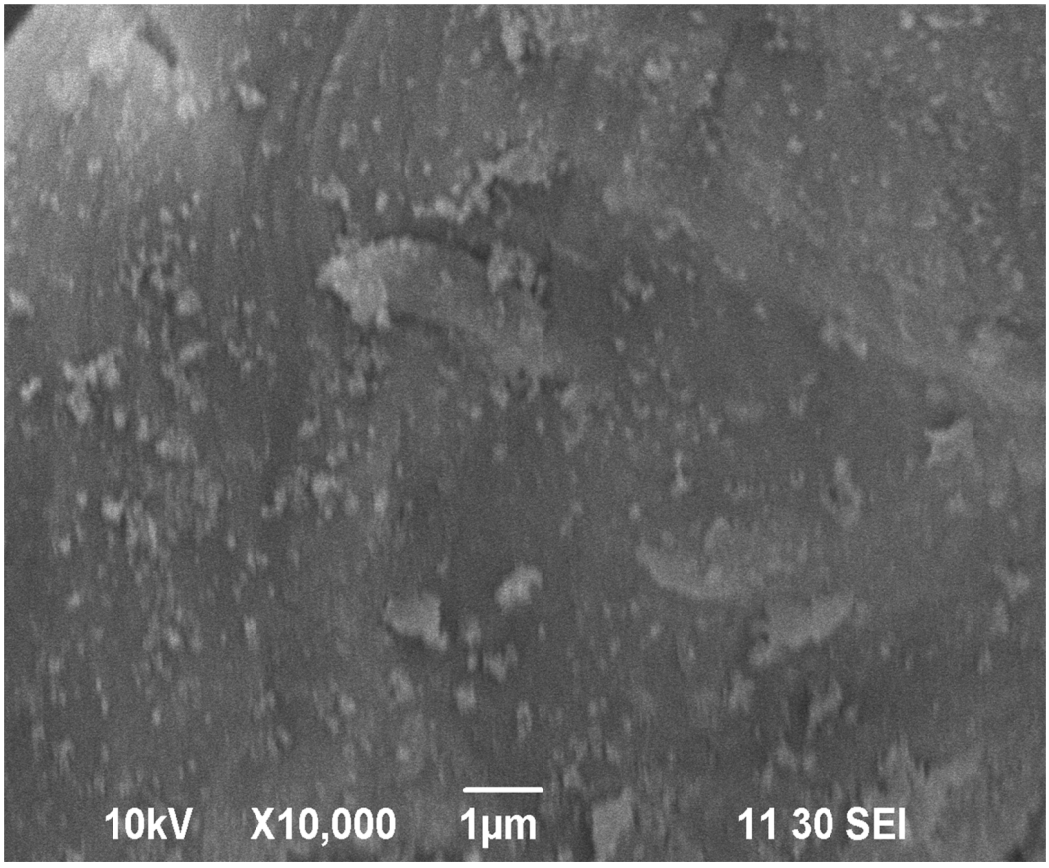

Figure 14: SEM of liquisolid tablet

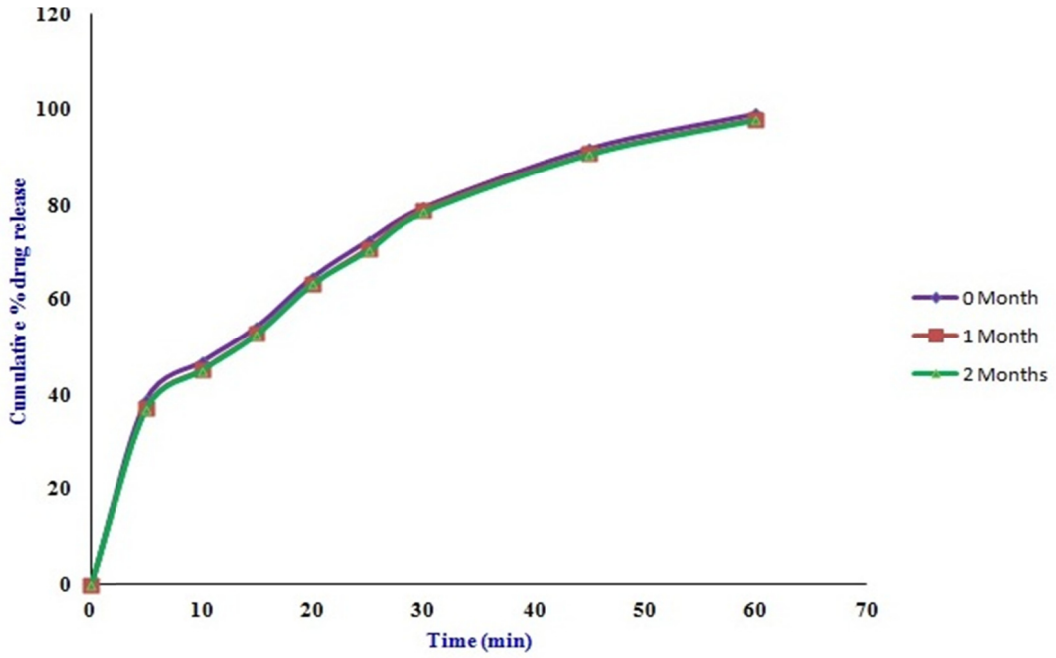

Figure 15: Comparison of *in vitro* dissolution profile (F20) of 0 month, 1 month and 2months (stored at 40^{o} C±2^{o} C and RH 75 %±5%)

CHAPTER X

SUMMARY AND CONCLUSION

CHAPTER - X

SUMMARY AND CONCLUSION

- The purpose of the study was to formulate liquisolid tablets of Paliperidone to improve the solubility and dissolution rate.
- The λ_{max} of Paliperidone was found to be 237nm in distilled water.
- The Paliperidone obeys Beer's law within the concentration range of 1-10 (µg/ml).
- The solubility studies were observed that the Paliperidone have highest solubility in Tween 80 compared to other non-volatile liquid vehicles.
- FT-IR showed that there was no interaction between the drug and excipients.
- The DSC thermogram of Paliperidone and liquisolid compacts, the sharp endothermic peak of pure drug appeared at 187^{o}C, whereas no such peak was observed in liquisolid formulation, which indicates that Paliperidone was molecularly dispersed and in an amorphous form.
- Flowable liquid retention potential (Φ-value) was used to formulate liquisolid tablets of Paliperidone.
- The twenty formulations were prepared using different concentration of drug in liquid medication, and different ratio of microcrystalline cellulose & aerosil 200 and sodium starch glycolate.
- The directly compressed tablets were prepared using microcrystalline cellulose and aerosil 200 and sodium starch glycolate, without addition of non-volatile liquid vehicle.
- The results of precompression studies which indicates that the prepared powder blend of all the formulations possess good flow properties.

- The postcompression evaluations such as hardness, thickness, weight variation, friability, drug content and disintegration test of all the formulated liquisolid tablets were within the acceptable limits.
- *In vitro* dissolution studies of all the formulations showed immediate release of drug. Among 20 formulations F20 was selected as a best formulation which had the better release of drug (99.24%) and subjected to further studies.
- The *in vitro* release studies revealed that the liquisolid tablets showed a faster drug release compared to the pure drug and directly compressed tablets.
- The results of the powder X- ray diffraction studies proved that the crystallinity of pure drug was remarkably reduced in the best formulation.
- The dissolution rate was increased, when the amount of non-volatile liquid increased from drug:Tween 80 ratio of 1:1 to 1:10.
- The dissolution rate (D_R) in 10 min, increased in linear manner with increasing ratio of drug: Tween 80.
- The selected formulation showed higher release profile than the pure drug and directly compressed tablets.
- The SEM image of the selected formulation showed complete disappearance of Paliperidone crystals.
- The selected formulation was found to be stable under the storage condition.

CONCLUSION

The liquisolid tablet technique can be effective way for dissolution rate improvement of water insoluble drugs such as Paliperidone. Tween 80 was used as a liquid vehicle. The liquid vehicle plays a contributing role in improving the dissolution profiles of a water insoluble drug in the liquisolid formulations, besides choosing a suitable liquid vehicle according to its viscosity and HLB value. Enhanced dissolution rates obtained in the present study in turn indicates increase in oral bioavailability due to increased wetting and surface area available for dissolution. Hence we can conclude that liquisolid tablets of paliperidone was prepared by using Tween 80 (1:10 ratio of drug and Tween 80) and 30 ratio of microcrystalline cellulose and aerosil 200 provide greater release of drug (99.24 % in 60 mins) among all the formulations, and this ratio can be used to enhance the solubility and dissolution rate of poorly water soluble drug paliperidone. This novel approach to the formulation may be helpful to improve oral bioavailability.

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